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General Medicine

The Headache of Solitary Cerebro-retinal Hypertension — GIRAUD, M. GASTON — *Schweizerische medizinische Wochenschrift*, 79: 884 (September 24) 1949.

The author was struck by the frequent association of poorly explained headache and an isolated rise of the retinal pressure. In individuals with a normal well balanced peripheral blood pressure isolated increase of the retinal pressure is often associated with cerebral symptoms, the essential and often solitary manifestation of which is headache of a constant or intermittent character. Like the headache in many cases of hypertension this headache may arise or become worse towards the end of the night or on waking up, and sometimes it is aggravated during the digestive periods, and by bending forward. In some cases it is increased on effort. The pain is dull, usually occipital, but often temporo-occipital or diffuse. Associated disturbances may include a cerebral impression of waves, a tendency to somnolence, incapacity to work, functional disturbances of the eighth cranial nerves in the sense of vertigo, a sensation of lack of equilibrium and tinnitus, and visual disturbances in the sense of temporary amblyopia, or photopsia. The headache rarely may be replaced by or associated with facial and cerebral congestive attacks, even leading to epistaxis or subconjunctival hemorrhages. Neurovegetative susceptibility is frequently found in young individuals, and certain metabolic and degenerative phenomena like hypercholesterolemia, discrete atheromatosis, and a tendency to calcifications in adults and old people. Middle-aged individuals are more frequently involved. Prolonged supervision is required as after a variable period of time a formerly completely latent or masked organic affection may become manifest, the isolated retinal hypertension having constituted its main prodrome. Even more slowly a generalized hypertensive process may develop. However, in some cases the syndrome remains benign and solitary for indefinite periods of time.

There is a relationship between systemic arterial and retinal blood pressure, the latter being 0.45 to 0.54 of the former; when the former increases the latter increases relatively more intensely. While the average ratio is 0.5 in the normal individual it reaches 0.66 in hypertension. Physiologic discordance between peripheral and retinal blood pressure is minimal, caused by physical work, prolonged lack of sleep, and anxiety, and transitory in character, but becoming protracted when the causal factors occur repeatedly. With age and diminished arterial elasticity the retinal pressure rises, but it falls in the very old; menstruation and pregnancy have only a slight influence.

The author then discusses the main clinical conditions which are capable of pathologic modification of the arteriocapillary retinocerebral tonus. First an essentially vascular process may produce discordance. With respect to local repercussions of systemic hypertension the author points out that discordance between systemic and retinal pressure can be spoken of only if the latter increases more intensely than would correspond to Bailliart's laws as happens particularly in malignant hypertension, in the form of an early stenosing syndrome or Riser's exudative syndrome of the posterior pole; the discordance is particularly marked in the early stenosing syndrome and its persistence in spite of rest is considered a sign of malignity. In another group of patients the systemic blood pressure is normal but slight metabolic or sclerogenic deviations are present, the vessels lack suppleness and atheromatosis appears in the older age group; the cholesterolemia is increased. The cornea may show a gerontotoxon, and calcification

of the pineal gland or the cerebral falx is frequently encountered. The syndrome in these cases includes subjective disturbances like headache and vertigo, humoral disturbances, and isolated cerebroretinal arterial hypertension.

In another group of usually younger individuals clinical analysis shows only a neurovegetative dystonia and regional dystonia may be spoken of in the presence of isolated retinal hypertension.

In the course of comas the retinal arterial tension is always elevated in the beginning; its decrease is a sign of severity and suggests irreversibility.

The dissociated increase of the retinal arterial pressure may result from a paraarterial process and the syndrome is then of an organic character; this occurs in disseminated sclerosis of the neuraxis but not in multiple sclerosis without a vascular factor, after head injuries in which such an increase has a medicolegal significance in that it speaks in favor of the authenticity of the subjective syndrome, and in inflammations of arachnoidea, glia and the sympathetic nerves, particularly of the posterior cerebral fossa. In epilepsy of the young the retinal pressure is lowered while it is increased in late epilepsy.

The next group involves intervention of peripheral extracerebral vascular factors in the absence of hypertension. Cervicocerebral circulatory disturbances with this manifestation include anatomic involvement of the internal carotid system with hypotension of the involved side, the syndrome of hyperreflexia of the carotid sinus which provokes a fall of the retinal pressure with or without peripheral hypotension, cervical vagosympathetic syndromes, and syndromes of hyperreflexia of the trigeminal-sympathetic system; the retinal pressure may rise in labyrinthine hyperreflexia, in nasal irritations and even in facial paralysis.

The influence of regional vascular territories as in Raynaud's disease and coronary disease is inconstant and variable.

The next group involves intracranial hypertension. Retinal hypertension will appear immediately when the intracranial hypertension develops rapidly, and with a delay when it develops slowly, as it is masked for a long time by a vasomotor reaction. Generally isolated hypertension of the central retinal artery precedes stasis but it may be lacking in tumors which ar centrally located or not in contact wit the venous pathways. Retinal hypertensio is frequent in tumors of the posterior, an less frequent in those of the middle an anterior fossa, so that dissociation betwee retinal and intracranial hypertension be comes more frequent.

Discordance may also be caused b venous hypertension, and there is agree ment that the retinal arterial pressur rises with pressure on the jugular veins.

Finally discordance may be of ocula origin as in retinal vascular sclerosis, em bolism, spasm, neuritis, glaucoma an other conditions.

In pseudosolitary retinal hypertensio masking the first stage of a progressiv affection from the vascular point of vie hypertension and from the extravascula one brain tumor must be taken into con sideration. Cerebroretinal hypertension a first manifestation of systemic hyperte sion is favored by faulty hygiene, cerebra or emotional overstrain and a neurovegeta tive disposition. With respect to tumor apart from true tumors encysted hemato mas, and foci of traumatic arachnitis mus be taken into consideration. Careful ob servation is required in all cases of isolate retinal hypertension.

In the second group the syndrome do not progress at all or does so only ver slowly. This group includes numerou cases in which the hypertension is actua ly secondary to a localized although som times unknown lesion which does not pr gress; this applies to labyrinthine dystoni sequelae of old otitis, vestibular sclerosi otosclerosis with reflex vascular reaction The sequelae of cerebral concussion, more accurately contusion also belong this group. Glial sequelae of an old inflam matory process may also have an irritati effect on the vessels.

In another group of apparently solita dissociated retinal hypertension vario and often minimal humoral and metabol disturbances are found; this group i cludes individuals with a tendency to h percholesterolemia, xanthomatosis or ca cification, those with discrete dyshepat (in these the headache particularly occu after meals), and those with hormonal a neurovegetative disequilibrium.

Temporary cerebroretinal hypertension with associated subjective and sometimes vasomotor disturbances may appear in the humorally unstable under the influence of various factors and also of allergic shocks, and on repetition a permanent syndrome may result. Intellectual and emotional strain may provoke early temporary syndromes while a permanent syndrome may supervene at the age of sclerosis. In summary minimal dystonia or vascular sclerosis may be the basis of apparently solitary dissociated cerebroretinal hypertension.

The syndrome of headache and solitary cerebroretinal hypertension should always be considered as alarming as it cannot be decided at its onset whether it will remain benign in character or will over a period of months or years develop into a malignant syndrome. In every case a complete clinical and metabolic analysis and prolonged careful supervision is indicated but the prognosis is not always serious, as the syndrome may remain stationary or may progress extremely slowly.

The Management of Abnormal Uterine Bleeding — SMITH, GEORGE VAN S.— *New England Journal of Medicine*, 241: 410 (September 15) 1949.

"Except for the stain of newborn females and the normal menstruation of constitutional precocity, all the rare cases of uterine bleeding during the period of childhood and preadolescence are but one manifestation of the precocious puberty associated with the following unusual conditions: certain cases of midbrain damage, Albright's disease, exceptional cases of tumor of the adrenal cortex, granulosa cell tumor of the ovary and, very exceptionally, chorioncarcinomatous teratoma of the ovary. The observation of premature growth and development, then, is the signal for immediate investigation and possible operation. Uterine bleeding after the establishment of the menopause is due most often to intrauterine or ovarian neoplasms, or both, rarely to cancer or sarcoma in the myometrium or to tubal cancer and very rarely to intrinsic vascular disease in the uterus. Between the menarche and the menopause the definite causes of abnormal uterine bleeding are intrauterine tumors and infections, pathologic pregnancy, both intrauterine and extrauterine, retained products of gestation, submucous fibroids, some estrogenic tumors of the ovary, diseases impairing the ability of the circulating blood to clot, and ovarian dysfunction. Placental dysfunction is, of course, involved in the bleeding of pathologic pregnancy. Less clearcut causes during this span of life are myometrial and subserous tumors, pelvic inflammations, endometriosis, retroversion of the uterus, nonestrogenic tumors of the ovary and uterine fibrosis, since these entities are often present without any abnormality of flow."

"According to the indications of present knowledge most, if not all, of the complications of pregnancy and the uterine bleedings that sooner or later accompany them are due to placental dysfunction. Because of ignorance concerning primary etiologies, the assumption has been made for years that any disease or disorder anywhere in the body may somehow lead to placental dysfunction. . . . Because of ignorance concerning specific primary etiologies, it is assumed that any disease or disorder may be an etiologic factor and as such may make ovarian dysfunction a cause of abnormal flowing in the nonpregnant woman, in addition to, or in the absence of, any of the causes listed above. This is the reason for including in the long range management of abnormal uterine bleeding the study and treatment of the whole patient, even though the beneficial effects may not become at once apparent. Especial and immediate attention is, of course, directed not only to the uterus and adnexa but also to the vulva, vestibule, urethra, vagina and cervix for sources of bleeding."

Surgery.—During the early teens operation is practically never necessary, in either the diagnosis or the treatment of this complaint, which is usually due to ovarian dysfunction of undeterminable cause and responds to progesterone therapy. "Some of these young women will have recurrent ovarian dysfunction that can be controlled by progesterone and finally ceases developing. Occasionally, however, one of them continues to have recurrent dysfunctional flowing, and cancer of the endometrium will be found during the twenties or early thirties."

"From the age of 18 on, surgical diagnostic and therapeutic procedures are, of course, increasingly indicated for a great variety of situations of which abnormal uterine bleeding is a sign." This brings the writer to an aspect of conservative pelvic surgery. "All gynecologists have the relatively frequent experience of seeing patients with this complaint who have had previous operations consisting of the excision of both tubes or bilateral tubal ligation, with or without ovarian surgery. These women are usually over 35 years old. A uterus capable of only one function, menstruation, yet still capable of being the source of serious or very serious trouble has been conserved." It is the writer's conviction that when operations involving sterilization are required, the continued health of these patients is more certainly assured by the removal of the uterus. "This prophylaxis eliminates not only menstruation with all its attendant unpleasantness, including premenstrual tension, which is so common to all ages, especially after 35, but also the potential source of tumors, benign and malignant. In retrospect it would have been life saving for many women. It almost completely eliminates soreness of the breasts, and fibrocystic changes in the breasts may disappear after it." The writer is advocating hysterectomy only in this limited group of patients and not the removal of any ovarian tissue except as indicated in the individual case. "When normal ovaries are conserved, menopausal symptoms do not occur prematurely." There are only three exceptions to the writer's proposal. One is that some women consider uterine bleeding an indispensable manifestation of their femininity. "Another is tubal interruption at the time of cesarean section. The third is when serious systemic illness requires limiting the amount of pelvic surgery to the necessary minimum." In connection with the question whether the hysterectomy should be complete or supracervical, the writer states that, in addition to those whose cancers of the cervix are missed at the time of the incomplete operation, at least 1 of every 100 women so treated will develop this disease some time later. "Moreover, 75 per cent of patients with cancer of the cervical stump die of the disease.

"After the establishment of the menopause any bleeding from the uterine cavity indicates the presence of a surgical condition. There is no place for the use of hormones in the treatment of postmenopausal uterine bleeding. The condition may be nothing more than an endometrial polyp which is likely to be found with the placental forceps or a clamp if missed by the curet. A palpable ovary in a postmenopausal patient is always pathologic. Even when no ovarian enlargement can be felt, the finding of hyperplastic endometrium signifies neoplastic ovarian activity. This may be benign but is always potentially malignant, as is the endometrium stimulated by it.

"Radiation.—The majority of women sterilized by radiation for abnormal bleeding associated with benign conditions, such as ovarian dysfunction and fibroids that are not submucous, get along very satisfactorily so far as later serious or disturbing pelvic troubles are concerned. That radiation is known to provide no immunity to the later development of genital cancer is no contraindication to its employment for cancer might have developed anyway. On the other hand, according to recent studies, irradiation itself is probably carcinogenic in the susceptible woman. . . . Enough patients do have pelvic trouble sooner or later, even up to 30 years, after radiation for benign conditions to make one wish that the original therapy had been surgical or had consisted of temporizing with medical management of the bleeding until ovarian function had become adjusted. Therefore, in general, it seems better to treat fibroids surgically, at the same time avoiding unnecessary castration in younger women. Similarly, it seems better in general to omit radiation for dysfunctional uterine bleeding and, instead, to employ surgery in selected cases and hormones in the others." By selected cases the writer refers to quite a few women between the age of 35 and the menopause who have dysfunctional bleeding, and often premenstrual tension as well, and also prolapse and vaginal relaxation with symptoms therefrom. "Many of these are best treated by vaginal, or complete abdominal hysterectomy without removal of the ovaries, along with reconstruction of the vagina. In the absence of the uterus, simple

ovarian dysfunction is harmless, causing little or nothing in the way of symptoms and no signs.

"Hormones.—Of the available hormones, progesterone and estrogen can be counted upon for predictable, immediate results in the control and regulation of dysfunctional uterine bleeding." Of the various ways of administering these ovarian hormones, the writer has found the following most effective:

"For the patient who has been flowing more than seven days, even for months, at the time the diagnosis of dysfunctional uterine bleeding is made 25 mg. of progesterone is injected intragluteally daily for five days during which the flow will slacken or cease. Two to four days after the last injection of this progesterone series a menstruation, often profuse, will ensue, ending in less than six days. The patient should be warned that the induced menstruation is the necessary evil of this efficient treatment. Normal cycles are likely to follow, for a time at least, but to make more certain of this result it is well to repeat the progesterone series at least once, starting 18 to 21 days from the onset of the induced menstruation. Should irregular bleeding persist between progesterone-induced periods it is certain that some pathologic condition besides an abnormally functioning endometrium is inside the uterus. In other words, the failure of progesterone to be immediately therapeutic, when given as described, points to an incorrect diagnosis and the necessity of investigation under anesthesia at once.

"For the patient whose cycles are of normal length but whose bleeding is profuse, or continues up to eight days, and who often has premenstrual staining as well, the simplest therapy is the oral administration of estrogen starting with the onset, or during the first two days, of the period. Estrone sulfate, in divided doses totaling 10 mg. daily, is taken for 25 days. To reduce expense, stilbestrol in daily doses of 5 mg., 10 mg. or even 25 mg. may be taken, on retiring, instead of estrone sulfate. Both of them may cause malaise in some women; in others a sense of well-being is produced. The occurrence of bleeding between the sixth day and the end of estrogen treatment indicates the presence of some undiagnosed condition within the uterus. Two to six days after the cessation of medication uterine bleeding will begin. Though not profuse, it occasionally lasts up to eight days. Thereafter, normal catamenia may or may not ensue. Should excessive flow again appear early in a cycle, the estrogen treatment may be started at once and continued again for 25 days.

"For this type of abnormal bleeding the progesterone series also has a place. If elected, it should be started between the eighteenth and twenty-first days of the cycle. Although in some women the ensuing catamenia may be profuse, it will not last so long. Moreover, there is a greater chance that normal catamenia will follow than after the estrogen treatment.

"For the woman whose cycles are disturbingly shortened, whether or not her bleeding is profuse or prolonged, the progesterone series is begun eight days before the expected onset of a period. Or the estrogen treatment is given beginning at the start of flow. Here again, uninterrupted bleeding during estrogen treatment or following a postprogesterone menstruation is indicative of an incomplete diagnosis."

The Treatment of Falciparum Malaria with Intramuscular Chloroquine — SPICKNALL, CHARLES G., TERRY, LUTHER L. AND COATNEY, G. ROBERT— *American Journal of the Medical Sciences*, 218: 374 (October) 1949.

The writers have treated 8 patients with falciparum malaria with chloroquine intramuscularly. "All of these patients acquired their infection in Africa and 6 had received suppressive or therapeutic quinacrine or quinine prior to admission to the hospital. The longest period that elapsed between the last administration of antimalarial drugs and treatment with parenteral chloroquine was 42 days; the shortest was 12 days. After the diagnosis was confirmed by blood smear each patient was given an intramuscular injection of 0.2 Gm. of chloroquine base in 5 cc. of sterile unbuffered aqueous solution according to the method of Culwell et al. One patient received an additional dose of 0.2 Gm. intramuscularly three days after initial administration of the drug." Daily parasite

counts were done on each patient and two to five days later each patient was given a routine course of oral chloroquine.

"No adverse local or systemic effects from the intramuscular chloroquine were observed in any of these patients; toxic effects following the parenteral administration of quinine or quinacrine are not infrequent. Rapid clearing of the parasites from the peripheral blood occurred although none of the patients had very high initial parasite densities. The most striking feature of treatment with parenteral chloroquine in this series was that in 6 of the 8 patients no asexual falciparum parasites were found in the blood after administration of the initial dose. The remaining 2 patients showed only 30 and 60 ring forms on the morning of the day further therapy was given. It is likely that the blood of these patients would likewise have cleared completely if further therapy had been delayed. Four of the 8 patients showed gametocytes in their smears after their blood was free of asexual parasites. Neither the intramuscular nor oral chloroquine had any apparent effect on the sexual forms.

"The clinical response of these patients to intramuscular chloroquine was likewise very striking. All of them became completely afebrile in one to two days and were markedly improved subjectively. Nausea and vomiting which had occurred in 3 patients subsided promptly following the initial therapy.

"The effect of previous antimalarial medication in these patients cannot be definitely determined. It is not likely, however, that this medication had any effect on their response to intramuscular chloroquine since there was a period of from 12 to 42 days from the time the patients last took quinine or quinacrine until chloroquine was given.

"It has been recommended that malaria with persistent vomiting, coma, impending coma or a high density of falciparum parasites in the blood smears (5 per cent or more of red cells infected) be treated with parenteral antimalarial drugs. Although none of the patients in this series showed a high parasite density, 3 of them had nausea and vomiting severe enough to prevent administration of oral medication. None of the patients had symptoms of cerebral malaria nor were any in coma." Since none of the writers' patients were critically ill, no definite conclusions can be reached as to the route of administration of the drug in this type of patient. One writer suggested that chloroquine could be given in a saline infusion intravenously over the course of three to four hours for the treatment of patients critically ill with falciparum malaria as carried out by Machella et al. with quinacrine and SN 6911. "The parenteral administration of chloroquine is not recommended for patients who can take the drug by mouth except for those who show very high parasite densities, as the absorption of chloroquine from the alimentary tract is usually very rapid."

Aureomycin in the Treatment of Infectious Diseases — ROSE, HARRY M. AND KNEELAND, YALE, JR. — *American Journal of Medicine*, 7: 532 (October) 1949.

The writers discuss the use of aureomycin in the treatment of infectious diseases.

Protozoal Diseases.—Rapid cures have been reported in 14 cases of amebic colitis with aureomycin by mouth. "Symptoms rapidly subsided and the stools became negative in a few days. Strains of amebas isolated from 3 of these were exposed to the drug in vitro and it was shown to have an amebacidal effect."

Diseases Due to Spirochetes.—Two cases have been reported of acute syphilis in which the patients were treated orally with aureomycin. "Results generally comparable to what would be expected with penicillin were obtained."

Bacterial Diseases.—Coccal Infections: Several writers treated 4 patients with pneumococcal pneumonia with aureomycin and reported results entirely similar to those obtained with penicillin. The present writers have had the same experience. Excellent results have been described in 1 case of meningococcemia. In regard to 60 cases of gonococcal urethritis, however, findings were different, and although the drug was effective it was distinctly inferior to penicillin. "It may be remarked, however, that small doses were administered in many of these cases."

Several writers have reported the successful use of aureomycin in localized staphylococcal infections including 2 cases with positive blood cultures.

"Bacillary Infections.—Among the most brilliant effects of aureomycin are those recorded in the treatment of brucellosis."

"Tularemia also responds very favorably to treatment with aureomycin."

"In view of its antibacterial powers in vitro it is not surprising that aureomycin has been tried in a number of infections due to members of the colon typhoid group." The writers have been unimpressed by the action of aureomycin in severe infections outside the urinary tract due to *Ps. aeruginosa* and Friedländer's bacillus in particular.

Disappointing experiences with typhoid fever and Salmonella infections have been reported. Several writers concluded that the efficacy of aureomycin in typhoid fever was very much less than that of chloromycetin.

Pulmonary Tuberculosis.—Several writers used aureomycin in the treatment of 3 young adult patients with extensive acute pulmonary tuberculosis. "The drug was administered mostly by mouth in doses of 2.0 Gm. to 4.0 Gm. daily for periods of from 34 to 94 days. In each case the sputum remained positive for tubercle bacilli and the patient showed no improvement either clinically or by x-ray during the treatment period. All 3 patients had a prompt therapeutic response to streptomycin after aureomycin was discontinued.

"Diseases Due to Rickettsiae.—Laboratory studies having indicated a powerful antirickettsial action of aureomycin, it followed that some of the first clinical trials of the agent were in this group of diseases. Since chloromycetin had already been proved to be effective in scrub typhus, it was hoped that aureomycin would act similarly. On the whole these expectations have been abundantly justified." Aureomycin has been found to be consistently successful in the treatment of Rocky Mountain spotted fever, in Q fever, in Brill's disease, in typhus, and in rickettsial pox. "Its action in all these various types of rickettsial infections has been remarkably uniform. Within 24 hours after the first dose there is an obvious change for the better in the patient's clinical condition. He appears brighter, 'toxemia' seems less, the temperature is lower and there is welcome relief of headache. At the end of 48 hours in most instances the temperature has reached normal levels, where it remains, and convalescence proceeds uneventfully. At times this does not take place until the third day but in any case all observers concede that aureomycin interrupts the course of every rickettsial disease thus far studied in dramatic style."

Diseases Due to Filtrable Viruses.—Evidence afforded by laboratory experiments warranted an early trial of aureomycin in lymphogranuloma venereum. The results of treatment in 35 cases have been reported. "Some of these patients had buboes, some acute proctitis and some rectal strictures. There was a remarkable and surprisingly prompt effect on the buboes. In a very few days they were materially shrunken and follow-up revealed that the remission was sustained. Acute proctitis responded equally well. The proctitis associated with rectal stricture also cleared although the chronic anatomic changes persisted."

The most unexpected finding in regard to this antibiotic was its curative effect in "primary atypical" or "virus" pneumonia. "Cases conforming to the accepted clinical pattern of atypical pneumonia, many of them with serologic confirmation of the diagnosis and most of them having been demonstrated to be unresponsive to penicillin, have almost without exception responded to aureomycin. In general the type of response resembles that seen in rickettsial diseases, particularly Q fever. That is to say, within 18 to 24 hours there is a definite improvement in the patients' general clinical condition, with lessening of fever, cough, headache and 'toxemia.' Ordinarily the temperature reaches normal levels at the end of 48 hours and convalescence proceeds smoothly." In the writers' experience, if the treatment is stopped at this juncture a relapse will occur but this may again be brought under control by readministration of the drug.

Ocular Conditions.—Several writers described the use of aureomycin mainly as a local application in the form of aureomycin borate, 0.5 per cent solution, in a wide variety of ocular infections. "Excellent results were described in conjunctivitis due

to staphylococcus, pneumococcus, *H. influenzae* and Morax-Axenfeld bacillus. Reports of several virus diseases of the conjunctiva and cornea were also included. The drug appeared effective in inclusion conjunctivitis and in 1 case of trachoma. It was also favorably reported in herpetic conjunctivitis. . . . Only 8 of 27 patients with epidemic keratoconjunctivitis appeared to benefit from the treatment but . . . . even so, aureomycin was more effective than any other agent thus far studied."

Miscellaneous Conditions.—Seven patients with granuloma inguinale have been treated orally with aureomycin and all of them showed a very satisfactory response.

In the writers' experience as well as in the hands of others aureomycin has had equivocal or negative effects in infective hepatitis and infectious mononucleosis. Although the evidence was not absolutely clearcut they concluded that it was not effective in the common cold. "It has been tried in a number of conditions of undetermined etiology such as rheumatoid arthritis, Hodgkin's disease, periarteritis nodosa, lupus erythematosus disseminatus, ulcerative colitis and Guillain-Barré syndrome without beneficial results. Its action in herpes zoster appears to be equivocal." In the writers' experience herpes simplex is unaffected.

A variety of dosage schedules with the oral preparation have been described. The antibiotic is now put up in 250 mg. capsules and it has been the writers' habit to regard 4 Gm. per day (1 Gm. every six hours) as the "standard" dose for an acutely ill adult of average size. At times when the condition seemed critical they have increased this to 6 Gm. the first day. "If the result of treatment is favorable this dose is reduced after two or three days to 2 Gm. or even lower. If nausea is a prominent feature smaller doses at shorter intervals may be given. The taking of milk, aluminum hydroxide gel, phenobarbital, etc., along with the drug has proved helpful. It is very uncommon to be compelled to discontinue treatment altogether on account of nausea.

"For intramuscular injection 30 to 50 mg. of the drug in 3 to 5 ml. of fluid together with procaine may be given at six hourly intervals. . . . This is a painful proceeding and if buffers are employed to diminish the acidity it must be remembered that the antibiotic rapidly loses its potency in solution at a neutral or alkaline reaction. A new vehicle for its intravenous administration, L (–) leucine, has recently been introduced. . . . In 5 ml. of this diluent (containing 131 mg. of leucine) 100 mg. of aureomycin hydrochloride may be dissolved. This can be injected directly at a very slow rate or added to an infusion of isotonic dextrose or saline. As much as 400 or 500 mg. every 12 hours may be given to very seriously ill patients. On the whole, oral administration has obvious advantages."

"Oral administration of aureomycin is frequently accompanied by nausea and occasionally by vomiting and a metallic taste in the mouth. Females appear more susceptible than males; more than half of the women patients may be quite distressed by these manifestations although their intensity usually diminishes if treatment is continued. The drug also has a slightly laxative action and the passage of an increased number of soft, bulky stools is frequently observed. True diarrhea is extremely rare." The writers have observed 3 instances of transitory vaginitis and a small number of cases of glossitis.

In the writers' clinic 1 case of complete neutropenia occurred in a dermatologic patient after prolonged administration of aureomycin.

Survival After Recent Myocardial Infarction — KATZ, L. N., MILLS, G. Y. AND CISNEROS, F. — *Archives of Internal Medicine*, 84: 305 (August) 1949. (Published October, 1949.)

"The results of an analysis of 507 cases of recent myocardial infarction are presented. The purpose of this study was to determine the factors concerned in long term prognosis.

"It was found that the mortality rate was greatest in the first two months and lessened progressively. The mortality rate continued to be high for the first year and then remained fairly steady from the second to the fifth year. By the end of the fifth to the sixth year, 81 per cent of the patients were dead. About one fourth of the patients died in the first two months,

about one half had died at the end of a year, about two thirds at the end of the third year and approximately four fifths at the end of five years. Thus, the survival rate varied from 72 per cent for the first two months and 55 per cent for the first year to 16 per cent for five years.

"Of the 52 patients who died after the second month following infarction in which the cause of death was known, 19 per cent died of heart failure, 6 per cent of pulmonary embolism, 65 per cent of a new myocardial infarct and 10 per cent of miscellaneous causes. There were no deaths after the first two months from cerebral apoplexy or renal insufficiency." The writers conclude, therefore, that a new infarct is hazardous, and, while it may occur at any time during the five year period, it is most frequent in the first year of the illness.

"Hypertension on admission had no effect on the mortality rate in the first two months but caused a slight increase, of questionable significance, in the long term mortality.

"The presence of known angina pectoris at the time of admission and up to one month preceding admission had no deleterious effect on the immediate mortality in the first two months, but the average duration of life of those who died after two months was somewhat shortened.

"The presence of heart failure on admission sharply increased the immediate and over-all mortality rate and noticeably shortened the duration of life of those who died after two months. It is obvious that heart failure affects unfavorably the immediate and long term prognosis of recent myocardial infarction.

"The presence of diabetes mellitus increased the mortality rate in the first two months, as well as the over-all mortality rate. However, the long term mortality rate was not greatly altered. The presence of diabetes, while not increasing the mortality rate after two months, led to an earlier death among those who died. Diabetes also reduced the duration of life of those known to have died even more strikingly in the whole group, suggesting that in the group who died within two months the ill effects occurred sooner than in the whole group." Therefore the writers conclude that the ill effects of diabetes manifest themselves earlier in the period after infarction and that the later prognosis is no worse than that for the entire group.

"When low voltage, sinus tachycardia, heart block or ectopic rhythm was present in the electrocardiogram on admission, the mortality rate in the first two months was definitely increased, but the mortality after the first two months was not significantly altered in this group. Thus, patients in this group who survived the first two months had as good a prognosis as the entire group. The absence of low voltage, heart block, ectopic rhythms and sinus tachycardia led to a much better immediate prognosis, but the long term prognosis was no better than that for the whole group.

"Patients who were symptom free on admission had an immediate mortality rate little different from that for the entire group, but the long term mortality rate was obviously better. Thus, the over-all mortality rate was less than that for the whole group. The average duration of life of those who died was considerably prolonged." Therefore the writers conclude that those who are asymptomatic on admission have a definitely more favorable outlook after the first two months.

"The mortality rate for the first two months, after the first two months and for the entire period increased with each succeeding decade. Older patients were more adversely affected by myocardial infarction than the younger ones.

"The immediate mortality rate was greater in women than in men, but after the first two months the mortality rate was less for women than for men. However, the over-all mortality rate was higher for women than men.

"Although the mortality rate in the first two months was little affected by the location of the infarct, the mortality rate after the first two months was definitely less for infarcts on the lateral wall than for those on the anterior or the posterior wall. Little difference was found in the mortality rate after two months between infarcts on the anterior and those on the posterior wall. The mortality rate was greater for the whole group when the electrocardiogram was classified as an atypical coronary pattern."

The Problem of the Transmission of Immune Antibodies from the Mother to the Child — SCHUBERT, J. AND GRÜNBERG, A. — *Schweizerische medizinische Wochenschrift*, 79: 1007 (October 22) 1949.

Animal experiments must be used cautiously in the evaluation of the problem of the transmission of immune antibodies from mother to child because of the differences in the anatomic structure of the placenta in man and animals, and the authors therefore limited their studies to human material. Because of good antibody formation after vaccination, great accuracy and specificity of the determination in vitro, insignificant reaction, and harmlessness or even usefulness of the vaccination for the mother, the flagellar H agglutinin of typhoid fever was used for the studies; the authors are aware of the fact that a rather complex antibody was used the transplacental passage of which is made difficult by the size of its molecules. Theoretically, immunity of the newborn may be produced by fetal antibody formation on the basis of diaplacental passage of antigen, by passage of maternal antibodies into the fetal circulation, by antibodies received with the maternal milk, by antibody formation in the placental tissue, or by heredity of a constitutionally produced resistance.

The authors used a single intracutaneous injection of 0.1 cc. of a formolized monovalent typhoid fever vaccine containing about 500 million germs on women during the second half of pregnancy. More than 80 women were thus vaccinated without systemic reactions; the local reaction was limited to a hyperemic infiltrated cutaneous infiltration of five days' duration. About 40 of these women delivered in the clinic and systematic studies were made on colostrum, milk, venous and umbilical cord blood, placenta, amniotic fluid, and retroplacental blood. The agglutinin titer was determined with the Widal-Ficker method, beginning with a dilution of 1:5 and increasing in a geometric series. Only the flagellar H agglutinin was studied systematically, as the somatic O agglutinin titer is low and as the finely granular O agglutination is difficult to read in cloudy fluids like milk. Before titration of the agglutination the material was centrifuged for 30 minutes at 3,000 revolutions, and if it showed an acid reaction it was neutralized in order to prevent spontaneous acid agglutination.

In addition 3 newborns were also vaccinated, and 2 pregnant women and 2 newborns were passively immunized by a blood transfusion from a nonpregnant woman of the same blood group with a titer of 1:5,000.

In the blood of the vaccinated women the agglutinins first appeared between the ninth and eleventh day, reached a stable level in rapid ascent, stayed at that level for several weeks, and then showed at first a fast fall and later a slow fall, but were still demonstrable in considerable amounts after several months. In 1 case an almost explosive inundation of the blood with agglutinins was observed on the eighth day a few hours after a cesarean section and was attributed to nonspecific activation by absorption of blood clots. Usually a titer of 1:640 or 1:1,280 was reached, and once it reached 1:10,000, but in some cases it was only 1:20; 2 individuals showed complete anergia, 1 of them being a woman with excessive anemia and the other with chronic puerperal endometritis and epilepsy.

The production of agglutinins is definitely not diminished during pregnancy, but even seems to be more active, particularly in the younger age group. Any marked influence of labor and puerperium on the once stabilized titer was not demonstrable; in 3 cases the retroplacental blood was examined and showed the same titer as that from the elbow vein. Although a great deal of antibodies is lost through colostrum and milk the titer does not change during the puerperal period, indicating the cellular origin of the antibodies. In the colostrum the agglutinins were present in particularly high amounts, frequently in a titer of 1:20,000, and once in a titer of 1:500,000, with a serum titer of 1:2,500. The agglutinins appeared in the colostrum at the same time as but not earlier than in the blood; the rise takes place in a parallel manner, but once the serum level is established after about two weeks the colostrum titer continues to rise. Repeated complete expression of the breast may lower the titer, probably

lue to dilution. The colostrum always con-ains a large amount of globulins. The ag-glutinin titer decreases with increasing milk production but the absolute amount of antibodies does not decrease at least at first. The agglutinins are usually demon-strable in the milk until three weeks after delivery; the opinion that only the colos-rum contains immune antibodies is defi-nitely erroneous. The serum titer does not decrease even when abundant milk with a high titer is secreted. When vaccination was done shortly before delivery so that at the time of appearance of the aggluti-nins in a circulation lactation was already active the titer in the milk did not reach that of the serum, but when delivery took place during the ascending part of the blood curve (10 to 20 days after vaccina-tion) the milk titer was maintained for at least a week at the level of 1:320 or 1:640. There was no difference in the titer of the milk from either breast, even when vaccination was done in the skin of one breast area. When 2 anemic pregnant women were given transfusions with blood with a titer of 1:5,000 their blood titer amounted to 1:160 and 1:80 respectively, with colostrum titers of 1:40 and 1:20 respectively; after five days the blood titer fell to 1:40 and 1:20 respectively and the colostrum titer to 1:5. This seems to prove that the antibodies reach the milk from the blood. The higher antibody concentra-tion in the colostrum may be explained in two ways: either stagnation leads to re-absorption of water and increased protein concentration, or primarily more globulins and antibodies are transmitted to the colos-rum; the first explanation seems more likely. At least during the first week of life the infant receives large amounts of antibodies with the milk but it has to be determined whether it is able to make use of them.

The antibody concentration was always found to be higher in the maternal than in the fetal part of the placenta, but it was lower than the serum concentration. Active participation of the placenta in agglutinin formation thus seems unlikely. The fetal portion of the placenta seems to act as neutral zone preventing the passage of complicated antibodies. No agglutinins could be demonstrated in amniotic fluid.

In the umbilical cord blood agglutinins were found in only 5 cases, corresponding to about 15 per cent; there was no relation-ship to the maternal titer, in that the pla-centa was impermeable in some cases with a high, and permeable in some with a low titer. In 2 of these 5 cases the cord blood titer was the same as the maternal blood titer, and in 3 it was markedly lower. The possibility of blood mixture from a gross placental lesion could be ruled out by com-plement titration. The placentas showed no macroscopic pathologic lesions in the cases with positive agglutinin findings in the cord blood. Mechanical injuries to the placenta and infections like syphilis cer-tainly play a part; in 1 case of diaplacen-tal passage of agglutinins labor pains had been provoked unsuccessfully three times during the second half of pregnancy, and in 1 case of syphilis the agglutinins passed even on passive immunization of the mother (maternal titer 1:40 and fetal titer 1:10). The agglutinins stayed in the blood of the infants rather long; thus in a case with a cord blood titer of 1:160 after 12 weeks a titer of 1:40 was still present. Undoubtedly passive immunity is dealt with in the infants. Three newborns were vaccinated with the same amount as the adults and showed a weaker local reaction than the adults and no agglutinins in the blood. After passive immunization of the newborn by transfusion with blood with a titer of 1:5,000 the agglutinins disap-peared much faster. The possibility that in diaplacental immunization passage of antigen is dealt with and that the fetus responds in 15 per cent of the cases can-not be ruled out. In the breast secretion of the newborns the serum of which con-tained agglutinins no agglutinins and only insignificant traces of globulins could be demonstrated.

The blood of the newborns was ex-amined at the age of 1 week and no ag-glutinins were found even on nursing with a milk high in such agglutinins unless such agglutinins had already been present in the umbilical cord blood, and no increase of the titer was observed in the infants whose cord blood contained agglutinins. As the babies usually nurse only from the second day on and as it seemed feasible that the intestinal mucosa is permeable only immediately after birth 3 newborns were

given about 5 cc. of a colostrum with a titer of 1:320,000, starting three hours after birth; serum determinations for agglutinins were negative three days later. The authors' studies showed in all cases that the agglutinins ingested with the milk pass the intestinal tract and are demonstrable in the stools of the infants, often with the titer the breast milk showed the day before, and sometimes with a higher titer, demonstrating agglutinin concentration after water absorption. The Pandy reaction of the stools of infants, particularly during the first week, is frequently intensely positive, demonstrating unchanged globulins. In vitro peptic digestion destroys the efficacy of the agglutinins contained in milk rapidly, within 20 minutes, and boiling destroys it rapidly and completely, while tryptic digestion does not damage the agglutinins to any considerable extent.

As even large amounts of agglutinins do not pass from the intestine into the blood of the infant although they are not destroyed by digestion, the question may be raised whether nursing might not be harmless in erythroblastosis, at least with respect to the agglutinins. Spontaneous delivery acts as mild nonspecific activation of the blood titer of agglutinins, but less so than parenteral injection of 0.5 cc. of milk. In a case of cesarean section the blood titer showed a striking increase, probably due to anesthesia and autohemotherapy.

Diaplacental immunization of the fetus against tetanus has been recommended and diaplacental passage of antitoxins is certainly much easier and has been proved for diphtheria antitoxin. Ramon demonstrated diaplacental passage of staphylococcic antihemolysin in man. The authors' studies demonstrate that diaplacental passage of agglutinins is the exception rather than the rule, and that they do not pass into the blood even from the milk. Diaplacental passage could be obtained only by loosening of the placental barrier, and such an intervention is not feasible because of harmful sequelae. On the basis of histologic findings of a direct contact between maternal and fetal blood in places as more or less normal condition, and of the authors' observations the following conclusions with respect to antenatal care of erythroblastosis seem justified: It may be assumed that the conditions for the ag glutinins are similar to those for the ty phoid fever agglutinin, and the main danger is therefore constituted by the incomplete (univalent) antibodies the diaplacenta passage of which has been established. Physiologic disturbances of the placental barrier can be aggravated by mechanical injuries, provocations and expressions. Therefore, premature provocation of labor would be contraindicated in erythroblastosis and metreurysis or cesarean section would have to be considered. Delivery should be as rapid and gentle as possible the cord should be ligated rapidly, and delivery of the placenta should be carried out with all care in view of future pregnancies. For hastening of repair of placental lesions substances favoring blood coagulation might be useful, including calcium and vitamins K and C, and also substances which strengthen the vascular wall like vitamins C and P, which support proliferation of the trophoblast like estrin, and which reduce permeability of the connective tissue like antihyaluronidase. The agglutinins would have to be feared less with respect to nursing, and with respect to the univalent antibodies boiling of the milk during the first two to three days might be sufficient.

The Treatment of Snake Bite Poisoning
—Chotkowski, L. A. — *New England Journal of Medicine*, 241: 600 (October 20) 1949.

"Only two poisonous snakes, the copperhead and the rattlesnake, both members of the pit viper family, are found in New England, the habitat of the two other poisonous snakes in the United States, the moccasin and the coral snake, being warmer climates.

"The typical pit viper bite reveals a pattern of two prominent fang marks and is associated with immediate pain and extensive edema. If these findings are absent the bite can be considered harmless (that is, in New England)."

"Once the fact has been established that one is actually dealing with the bite of a venomous snake, the treatment falls into four general phases—namely, first-aid therapy, the use of antivenin, the prophylaxis of infection and the application of

general supportive measures. It seems that prompt first-aid management is of considerable importance in the prognosis of these cases. Ideally, the limb is placed at rest in a dependent position, a tourniquet lightly applied proximal to the bite, and immediate incision and suction of the incision performed as soon after the bite as possible. . . . Multiple incisions and suctions should be made in a staggered fashion, circling the limb at higher levels as the edema advances. . . . It is suggested that in a severe bite, 50 to 100 small incisions be made and suction continued for 20 minutes every 2 hours for 36 hours. The tourniquet is applied lightly, since absorption of the venom is by way of the lymphatic rather than, primarily, the venous system. The copperhead bite however, usually does not appear to be fatal in adults, and such vigorous treatment may probably be deferred. Other local therapy such as the use of potassium permanganate crystals no longer seems indicated.

"A polyvalent antivenin derived from horse serum and said to be effective for all North American poisonous snakes, except the coral snake, should be given immediately in the usual 15-cc. dose. It is suggested by some workers that 5, 10 or even 15 doses be used in severe bites and that a single 15-cc. dose is practically of no value. . . . In children, since the body weight is less and the concentration of venom per kilogram thus greater, a larger dose of antivenin is necessary than in the adult. . . . Since antivenin is a product of horse serum, its administration should be preceded by the usual test for sensitivity. Antivenin may be administered subcutaneously, intramuscularly or, if symptoms are severe, intravenously. It is preserved in a powdered state and must first be dissolved in distilled water. If the patient is seen within the first two hours, half the initial dose—that is, 7.5 cc.—should be injected locally. The amount of antivenin in one 15-cc. ampule is said to neutralize the amount of venom necessary to destroy 50 pounds of body weight. On the basis of this ratio it seems that three or four ampules contain sufficient antivenin for the ordinary case. . . . After bites from rattlesnakes and larger moccasins, in general, a larger dose is indicated."

The use of antibiotics—such as penicillin—is indicated in the prophylaxis of secondary infection. "Tetanus antitoxin is also indicated in view of the frequent occurrence of tetanus following snake bites. Wet dressings are suggested for ulcerative areas that may develop.

"General supportive care consists chiefly in the treatment of shock, if it occurs, with the use of blood or plasma, preferably blood. Since many patients have experienced either vomiting or diarrhea, fluid and electrolyte balance must be adjusted. Hemolytic anemia in severe rattlesnake bites may produce a drop of 2,000,000 in the red cell count."

"The most striking evidence of a pit viper bite is the characteristic edema, usually painful, which develops almost immediately after the bite. This is due to the effect of the injected venom. . . . It is a violent irritant, producing a proteolytic and cytolytic effect on the tissues locally and a hematoxic or hemolytic effect on the red blood cells systemically. . . . In view of the obnoxious characteristics of this venom one might certainly hesitate before using mouth suction in removing it from the puncture wounds, particularly in the presence of gingivitis or similar oral lesions. The application of a square of rubber over the bite to protect the mouth has been suggested in emergencies."

"The prognosis for copperhead bites in adults properly treated should be good."

The writer presents the following case:

"J. L., a 19 year old high school student, was admitted to the emergency room of . . . . hospital at 12:30 A.M. on May 2, 1949. He stated that about ½ hour before admission he had been fishing in a local reservoir, an area known to be infested with copperhead snakes. While walking about the shore of the reservoir, he felt a sudden needle-like jab in his right ankle. In the darkness it was impossible to identify the snake that had bitten him, but in view of the presence of copperheads in this area and in the absence of a rattle it was assumed that the snake was a copperhead. The patient did nothing in the way of first aid for the bite, reporting directly into the hospital. Being alone, he rode in on his bicycle, the entire trip taking about 20 minutes. While riding his bicycle, he noted pain and stiffness in the

ankle and a slight chilly sensation, but no shaking chills or prostration.

"On admission he appeared anxious and in some discomfort owing to the bite. Examination revealed a well developed, well nourished boy. There were two pinpoint puncture wounds, approximately 1 cm. apart, situated on the inner surface of the right ankle approximately 1 cm. behind the internal malleolus. There was a bloody, serous discharge from both wounds. There was also at this time, approximately 20 minutes after the bite, swelling, redness and tenderness of the entire ankle extending upward to about 7.6 cm. above the malleolus. Palpation in the popliteal space was slightly tender, and there was tenderness extending up the inner aspect of the thigh to the groin, where the lymph nodes were slightly enlarged and also tender.

"The temperature was 98.6° F., the pulse 78, and the respirations 20. The blood pressure was 118/60.

"Examination of the blood showed a hemoglobin of 92 per cent (14.4 Gm.) and a white cell count of 11,300, with 68 per cent segmented and 11 per cent nonsegmented forms and 21 per cent lymphocytes. The urine had a specific gravity of 1.024, with negative tests for albumin and sugar, and the sediment contained 0 to 1 pus cells and 0 to 1 red cells per high power field. The prothrombin time on the morning of admission was 100 per cent of normal (16 seconds), and the sedimentation rate 4 mm. per hour. The blood serologic findings were negative. The nonprotein nitrogen was 42 mg. per 100 cc.

"On admission to the emergency room, a tourniquet tight enough to prevent venous return was placed about the patient's thigh, and two linear incisions about 2 cm. in length were made over both puncture holes. These incisions were then irrigated with saline solution and were suctioned thoroughly for about 15 to 20 minutes hourly for the next 10 hours. The tourniquet, which at first had been applied at the thigh, was reapplied at the ankle just above the line of edema. After an intracutaneous test for horse serum sensitivity, to which the patient was negative, 15 cc. of polyvalent snake serum was injected intramuscularly. At the same time he was given 3,000 units of tetanus antitoxin; 1 cc. of penicillin in oil (300,000 units) was given twice daily during the period of hospitalization. Pyribenzamine, 50 mg., was given four times daily. On admission the right ankle was 30.5 cm., the left ankle 27.9 cm., the right calf 36.8 cm., and the left calf 36.2 cm. in circumference; on the following day respective measurements were 28.6, 27.9, 36.8 and 36.8 cm. On the leg itself, which was kept flat, there appeared a yellow-blue, very tender discoloration along the lymphatic circulation of the inner aspect of the calf and inner aspect of the thigh. This discoloration gradually became darker but less tender in the next 48 hours.

"In view of the benign course that the patient was running, he was discharged from the hospital on the third hospital day approximately 60 hours after admission.

"At home he was allowed to be up and about, and under this treatment the residual swelling in the right ankle disappeared in about one week. The discoloration along the lymphatics lasted approximately two weeks. When last seen in the office, approximately three weeks after the bite, the patient felt entirely well, and the leg appeared normal. There was a moderate urticarial serum sickness reaction one week after injection of the serum."

Aureomycin in the Treatment of Tularemia—Ransmeier, John C., Price, Harry J. and Barnes, Zerney B., Jr. — *American Journal of Medicine*, 7: 518 (October) 1949.

The writers' results with aureomycin treatment of 3 patients with tularemia at Lawson Veterans Administration Hospital and Grady Memorial Hospital are described.

"Case 1.—Tularemic Pneumonia: A 37 year old Negro skinned and dressed two wild rabbits on December 4, 1948. On December 9 he noted malaise followed by a shaking chill, generalized aching and headache. The following day his temperature was 102° F. Fever continued and he remained in bed. On December 13, the fifth day of illness, he was admitted to Lawson Veterans Administration Hospital.

"The patient appeared moderately ill. He was oriented but lethargic. Oral temperature was 99.6° F., pulse rate 74, re-

spiratory rate 24 and blood pressure 100/70. There was a crusted ulceration measuring 3 mm. in diameter over the dorsal surface of the distal interphalangeal joint of the left thumb. No surrounding tenderness, erythema or edema were present. This lesion had been present since mild trauma three weeks previously. Nontender, firm lymph nodes measuring about 1 and 1.5 cm. were palpable in the left and right axillas, respectively. Except for occasional nonproductive cough, examination of the chest was negative and the rest of the physical examination was noncontributory.

"Examination of the blood on the sixth day of illness revealed 7,950 leukocytes per mm. of which 88 per cent were neutrophils. The urine had a specific gravity of 1.030; it contained no sugar and 3+ albumin. An uncentrifuged specimen showed 3 to 6 red cells, 5 to 10 white cells and a few granular casts per high power field.

"On the sixth day of disease the temperature rose to 105° F. and the respiratory rate to 32. Cough became more frequent and the patient appeared seriously ill. Although physical examination of the chest was negative, x-ray showed confluent patchy consolidation in the peripheral portion of the right upper lung field with extensive right hilar lymphadenopathy. The sputum smear and culture revealed only normal bacterial flora; culture for tubercle bacilli was later reported negative. Three blood cultures in tryptase phosphate broth were negative December 14 and 15.

"The presence of pneumonia associated with a history of rabbit contact suggested the diagnosis of tularemia. . . . The temperature followed a typhoidal course ranging from 103° to 105° F. without remission. On the seventh day of illness oral administration of aureomycin was begun in doses of 1.5 Gm. every six hours for four doses, then 1 Gm. every six hours. Within 24 hours the temperature declined to 99.8° F. but rose again to 101° F. then dropped to 99.2° F. on the ninth day of disease. The respiratory rate fell to 20, the cough decreased and the patient was greatly improved. Although he continued to feel well except for residual weakness, the fever then began to increase daily. On the twelfth day of illness the aureomycin dosage was increased to 1.5 Gm. every six hours but the temperature continued to climb reaching 103.2° F. on the fourteenth day. The patient did not appear very ill; his cough had almost subsided. The chest remained clear to physical examination and there was little change noted in the x-ray. The leukocyte count was 4,400 per mm. Aureomycin was discontinued after a total dosage of 35 Gm. Within 48 hours the temperature dropped to normal.

"The agglutination test with *B. tularense* antigen was negative on the sixth day of illness but became positive in dilutions of 1:1280 on the fourteenth day and 1: 2560 on the sixteenth day. Repeated agglutination tests with *Br. abortus* antigen were negative.

"The patient continued afebrile and improved steadily. Chest x-ray on the twenty-second day showed considerable clearing of the pulmonary consolidation and reduction in the hilar lymphadenopathy."

"This patient's condition was complicated by a urethral stricture and low grade urinary tract infection. . . . The stricture was dilated on the twenty-eighth day, followed by a brief febrile rise to 100° F. Urinary symptoms were relieved and the patient was discharged on January 8, the thirty-first day of illness."

"Case 2.—Ulceroglandular Tularemia: A 33 year old Negro cut his left index finger with a pocket knife about November 18, 1948. On November 20 he ate rabbit but denied handling the animal before it was cooked. His illness began abruptly on November 23 with headache and fever, followed shortly by a shaking chill. A few hours later a second chill occurred. Next day anorexia, nausea and vomiting appeared with another chill and severe headache. He remained at home, and fever, weakness, aching, anorexia and occasional nausea and vomiting continued. An infected ulcer developed on the finger at the laceration site and a tender swelling appeared in the left axilla. He was admitted to Grady Memorial Hospital on December 6, the fourteenth day of illness.

"The patient was acutely ill. Oral temperature was 102° F., pulse rate 112, respiratory rate 20 and blood pressure 120/80. On the left index finger there was a crusted ulcer measuring 1 by 2 cm. without surrounding induration or tenderness.

A firm tender node 2 cm. in diameter was palpable in the left axilla."

"Examination of the blood revealed 19,800 leukocytes per mm. with 65 per cent neutrophils. The urine had a specific gravity of 1.024; it contained no sugar and 2+ albumin. A centrifuged specimen showed occasional red cells and 5 to 7 white cells per high power field. Chest x-ray was negative. Two blood cultures in tryptase phosphate broth on the fourteenth day of illness and two on the fifteenth day showed no growth. Serum agglutinins for *B. tularense* were present in a titer of 1:80 on the fifteenth day and 1:160 on the sixteenth day.

"During the first 48 hours in the hospital the fever followed a septic course, reaching a peak of 104.2° F. on the sixteenth day of illness. Aureomycin was started orally at that time in doses of 1.5 Gm. every six hours and administered in lesser doses . . . . until the twenty-third day. A total of 19.5 Gm. was given.

"A remarkable clinical improvement occurred after the start of aureomycin therapy. Within 12 hours the temperature dropped to normal and did not rise above 99.4° F. thereafter. Coincident with the fall in temperature there was profuse perspiration and striking subsidence of symptoms. Malaise and aching disappeared, the appetite returned and strength was rapidly regained. Serum agglutinins for *B. tularense* rose to 1:320 on the seventeenth day and were present in a dilution of 1:640 on the twenty-first, twenty-fourth and twenty-seventh days. On the twenty-seventh day the agglutinin titer for *Br. abortus* was 1:160. The patient was allowed out of bed on the eighteenth day and was increasingly ambulatory thereafter. The finger ulcer healed in a few days. By the twenty-fourth day the axillary node had decreased to half its original size and the patient was discharged on December 21, the twenty-eighth day of disease. When he was seen in the outpatient clinic on January 7, the axillary node was no longer palpable and he appeared completely recovered."

"Case 3.—Ulceroglandular Tularemia: A 44 year old Negro incurred an abrasion of the right index finger while hunting on November 23. He killed and dressed five wild rabbits. The injured finger became painful on November 26 and he developed headache, malaise and chilly sensations. Next day he was much worse and remained in bed. After three or four days the finger lesion drained a small amount of pus and a tender swelling appeared in the right axilla. Five or six days later there was some improvement and he was ambulatory although weakness, malaise and low grade fever persisted until admission to Grady Memorial Hospital on December 8, the thirteenth day of illness."

"On admission the patient was only mildly ill. Oral temperature was 101.2° F., pulse rate 84, respiratory rate 22 and blood pressure 115/70. On the right index finger there was an indolent lesion measuring 1.5 by 1 cm. which was slightly elevated and indurated and covered by scaly epidermis. A tender nonfluctuant lymph node measuring 5 cm. in diameter was palpable in the right axilla. No other significant findings were noted.

"The leukocyte count was 21,550 per mm. with 74 per cent neutrophils. Urinalysis was negative except for occasional white cells in a centrifuged specimen. Agglutination tests with *B. tularense* antigen were negative on the thirteenth and fourteenth days of illness. Chest x-ray was negative on the thirteenth and twenty-first days."

"Aureomycin was started orally late on the thirteenth day of illness in dosage of 1.5 Gm. every six hours for four doses after which the dosage was reduced. . . . Within 24 hours after the start of therapy the patient felt better and in 48 hours the temperature dropped to normal. He was asymptomatic except for tenderness in the axilla. However, on the sixteenth day of illness the temperature rose to 99.4° F. and on the seventeenth day to 101° F. Serum agglutinins for *B. tularense* appeared in a titer of 1:80 on the eighteenth day. On the nineteenth day aureomycin was increased to 1 Gm. every six hours; but since the axillary node remained tender and gradually became fluctuant, the antibiotic was discontinued on the twenty-second day. Aspiration of the node was performed on the twenty-third day and 10 ml. of pus removed. Next day the temperature dropped to normal and remained so. Agglutinins for *B. tularense* reached a titer of 1: 160 on the twenty-fourth day, with

o cross agglutination of *Br. abortus* anti-
en. The axillary node was still palpable
ut the patient was otherwise asympto-
natic when discharged from the hospital
n December 22, the twenty-seventh day
f illness.

"The patient remained free of symptoms
xcept for swelling and tenderness in the
xilla. The node was again aspirated in the
utpatient clinic on January 4 and 11, 15
l. of pus being removed on each occasion.
n January 15, the fifty-first day of illness,
ontaneous rupture occurred after which
rainage gradually subsided. By February
, 68 days after onset, all induration in
e axilla had disappeared and the patient
as entirely well."

lumps Meningoencephalitis with and Without Parotitis — KILHAM, LAWRENCE — *American Journal of Diseases of Children*, 78: 324 (September) 1949.

"In the present study of 25 patients
ith mumps meningoencephalitis, 13 with
o enlargement of the salivary glands, con-
lusions were based on cases diagnosed by
eans of a combination of the newer tech-
ics of serologic study and virus isolation.
. . The patients presented were followed
i two Boston hospitals in 1948, a year par-
cularly suited to the study because of the
nusual prevalence of mumps in Massa-
husetts."

"Meningeal irritation was variously
arked by headache, nausea, vomiting and
uchal rigidity. A few children had con-
ulsions and delirium. One significant
ature was the impossibility of distinguish-
g by clinical means between the signs
nd symptoms of patients with mumps
eningoencephalitis and those of others
ho had serologically negative reactions
r mumps and such clinical diagnosis as
onparalytic poliomyelitis and lympho-
tic meningitis.

"Seven of 12 patients who had both
eningoencephalitis and parotitis showed
e two conditions on the same day. In 5
hers parotid swelling preceded encepha-
tis five to nine days and had subsided by
e time the patient came to the hospital.

"A few patients had sequelae. One, 2
1/12 years of age, had weakness of the
nterior part of the neck and abdominal
uscles when seen later in a clinic for after-care of poliomyelitis. A 4 year old boy had weakness of a leg a few weeks after his discharge from the hospital. Two patients were judged to have personality changes as a result of their illnesses, these being especially striking in a boy, 16 years old. The patients of this series ranged in age from 1 to 35 years, with 18 under 10 years and 5 who were 16 years or older. Most of the patients were male, only 5 of the 25 being female. The average duration of illness was eight days."

"A pronounced pleocytosis, with a high percentage of lymphocytes, characterized the spinal fluid of patients with mumps meningoencephalitis. Leukocytes exceeded 300 per cu. mm. in 19 instances and were more than 1,000 per cu. mm. in 9. No count fell below 100 per cu. mm. in the first week of disease, and one reached a peak of 2,920 cells per cu. mm. Every patient showed a 95 or greater percentage of lymphocytes at some time, although 4 of the 64 spinal fluids examined had percentages slightly below this figure. The leukocyte count tended to reach a high point sometime during the first week of the disease. Several lumbar punctures were ordinarily needed to bring out maximum values both for leukocytes and for total proteins. Maximum values for total proteins usually came later than those for leukocytes." Proteins were above 40 mg. per 100 cc. in 16 patients; 6 had values greater than 100 mg., and 1 patient had 253 mg. on the twelfth day. Leukocytes and total proteins of spinal fluids often persisted at abnormal levels after clinical recovery, in 4 patients for two weeks and more after onset and in 1 patient past the thirty-third day.

"The antihemagglutination and the complement fixation tests gave comparable results." One or both tests showed a fourfold and usually a greater increase in antibodies when serums of the acute and convalescent phases were compared for all patients, except for 1 patient for whom serums from only the acute stage of illness were available. "The first serum for this patient had a low titer of complement fixing antibodies but showed a twofold rise after two days and mumps virus was isolated from the spinal fluid." Two patients showed a substantial rise of antibody titer by complement fixation test, while both acute and

convalescent phase serums had identical titers by the antihemagglutination test. "The times at which antibody rises took place varied so greatly from patient to patient as to give no definite indication that one type of antibody rose in titer earlier than the other.

"Among patients with encephalitis serving as controls by reason of clinical differences in some and the uniform failure to isolate mumps virus, a number showed high titers of mumps antibodies in both acute and convalescent phase serums. A few might have shown a significant rise of mumps antibodies had the serums been collected at different intervals than they were." Spinal fluids of 2 patients were not unlike those of patients with proved mumps infections. Two patients with paralytic poliomyelitis also had high, unchanging titers of mumps antibodies, especially 1 patient, who had a history of exposure to mumps.

One patient was unusual in that encephalitis appeared three weeks after parotitis. "Serums from this patient collected three and six weeks after the onset of parotitis expectedly showed high antibody titers. The condition was not considered to be primary mumps meningoencephalitis because (1) the spinal fluid was unlike that of patients with proved mumps encephalitis, (2) for encephalitis to follow parotitis after three weeks is unusual, (3) the patient came from a locality where an outbreak of mild meningoencephalitis of known origin was prevalent and the spinal fluid was typical of those observed in the course of the epidemic and (4) attempts to isolate mumps virus from the spinal fluid were unsuccessful. A secondary or postinfectious type of encephalitis, however, is conceivable."

"Of 21 attempts to isolate mumps virus from patients with clinical mumps meningoencephalitis, all were successful. An initial belief that the first two or three days of the disease were most favorable for isolation of virus was not substantiated, since 4 strains were obtained on the fifth and sixth days when the proportion of failures was no greater." The persistence of an abnormal spinal fluid suggested that mumps virus could be isolated from the spinal fluid occasionally in the second week of disease or even later, but this was not determined, since, other than one specimen taken on the eleventh day, which proved negative, no specimens for virus isolation were collected after the sixth day. "All spinal fluids were subjected to at least 3 passages in embryonated eggs. Mumps virus appeared on the first passage in 5 instances, on the second passage in 4 and on the third passage, twice. Six attempts to demonstrate mumps virus directly in the spinal fluid by agglutination of hen erythrocytes were unsuccessful. The mumps virus in cerebrospinal fluid can withstand storage under dry ice for long periods, since the fluid of patient 25 yielded virus five months after first refrigeration."

One patient was of special interest, since mumps virus was isolated from the saliva on the second and fourth days of disease in spite of an absence of enlargement of the salivary gland, although orchitis developed on the sixth day. "Virus was not isolated from 4 other patients having no enlargement of the salivary glands when specimens were collected on the third to fifth days of disease.

"To test the hypothesis that invasion of the central nervous system is a primary feature of mumps infections, spinal fluids from 6 patients with early mumps parotitis and no evidence of meningeal involvement were examined for virus. The series of egg passages made with each specimen gave a negative result.

"A total of 12 patients served as controls for the group with serologically proved mumps meningoencephalitis: 6 patients with uncomplicated mumps parotitis and 6 with disease of the central nervous system determined not to be mumps by serologic test. Mumps virus was isolated from the spinal fluid of more than half of the patients with confirmed mumps infection of the central nervous system and in no instance from that of the control series."

Conclusions.—"As clinical findings are not sufficiently characteristic, mumps meningoencephalitis without glandular enlargement is to be recognized with certainty only through demonstration of a significant rise of specific antibodies when acute and convalescent phase serums are compared, unless mumps virus is isolated from the spinal fluid. Serologic diagnosis

readily accomplished by means of a relatively simple antihemagglutination test.

"In some instances, mumps virus is demonstrable in the cerebrospinal fluid as late as the sixth day of encephalitis and occasionally from saliva in patients with meningoencephalitis unaccompanied by enlargement of salivary glands.

"Mumps meningoencephalitis may be prevalent throughout the summer months. There is a suggestion that enlargement of the salivary glands is less frequent at this season."

Leukemia, Lymphoblastoma and Polycythemia Vera — LIMARZI, LOUIS R. —*Minnesota Medicine*, 32: 892 (September) 1949.

"There is no cure for leukemia, and the therapeutic agents used in the disease are palliative in their effect. Patients with leukemia are made more comfortable by treatment despite the fact that it may not prolong life materially. In general, the indications for treatment in the chronic forms of myeloid and lymphatic leukemia are the appearance of signs and symptoms of anemia, hemorrhagic manifestations, pressure effects from an enlarged spleen or from enlarged lymph nodes or evidence of leukemic infiltrations in other organs.

"Chemotherapy.—Arsenic in the form of potassium arsenite has been used in the treatment of chronic myeloid leukemia for many years. Arsenic administered by mouth over a long period of time has been followed by a gradual return of the leukocyte count to normal, associated with a rise in the hemoglobin and red blood cell count. The blood platelets are not depressed, and arsenic may be used in the leukopenic phase of the disease. The splenomegaly decreases, and the patient may appear clinically well. The initial dose is 3 to 5 minims of Fowler's solution in orange juice or milk, given three times daily after meals. After several days the dose is increased by 1 minim daily to the point of tolerance or the point at which the leukocyte count is normal. The serious objection to the use of Fowler's solution is development of toxic symptoms; namely, loss of appetite, nausea, vomiting, diarrhea, dermatitis, neuritis and renal irritation. The drug eventually has to be stopped in all cases, and this is usually because of its effect on the skin. Satisfactory remissions of from 3 to 18 months have been maintained with Fowler's solution."

"In selected cases of chronic myeloid leukemia, urethane will produce a rapid fall in the white blood cell count and a nearly normal blood pattern. The dose is from 1.0 to 5.0 Gm. daily administered by mouth (7 1/2 grain tablets or 5 grain enteric-coated tablets). It may also be administered parenterally, although the intravenous route is not without danger. Remissions in chronic myeloid leukemia may be maintained with urethane as long as a proper dose is given. If the drug is stopped or if the dose is decreased, the leukocyte count steadily and rapidly rises, only to drop again with institution of adequate urethane therapy. The red blood cell count and hemoglobin values are improved during this treatment." The enlarged spleen decreases in size, but in the writer's experience it never receded to its normal size. It is the writer's impression, from a study of approximately 100 cases of leukemia, that some patients are made chronically sick while on urethane therapy in spite of the decrease in the leukocyte count and the recession in the size of the spleen and lymph nodes. "Some patients experience anorexia, marked nausea and vomiting, or may show toxic symptoms in the form of anemia, agranulocytosis and thrombocytopenia. The drug may aggravate the gastrointestinal bleeding in cases of chronic myeloid leukemia. Urethane is generally more effective in chronic myeloid leukemia, although a reduction of the leukocytes to normal with a decrease in the size of the lymph nodes is frequently observed in chronic lymphatic leukemia." Acute leukemia is not benefited by the drug, although a temporary remission was induced in 2 cases.

Nitrogen Mustards.—"The dose of nitrogen mustard is usually 0.1 mg. per Kg. of body weight given intravenously daily for four to six days. Because of the rapid hydrolysis, the solution is freshly made by dissolving 10 mg. of the drug in 10 cc. of sterile isotonic solution of sodium chloride. The calculated dose is then immediately injected into the rubber tubing during the course of an intravenous infusion of saline solution in order to avoid its con-

tact with the patient's subcutaneous tissue or skin. Thrombophlebitis may also occur. Because of the toxic action of nitrogen mustard on the hemopoietic tissues, a complete blood count including a platelet count should be performed daily during the course of the treatment. Nausea and vomiting, often severe, are common in many cases one to three hours after the administration of the drug. Repeated remissions of 6 and 12 months have been obtained in several cases of chronic myeloid leukemia. Somewhat better results have been obtained in the treatment of chronic lymphatic leukemia. Practically all the patients treated have responded to the initial course of the drug with remissions which lasted from 2 to 21 months. Nitrogen mustards are of little or no value in acute leukemia. In general, nitrogen mustards are not superior to roentgen rays in the treatment of leukemia, although occasionally they are useful in radioresistant patients."

Folic Acid Antagonists.—"The folic acid antagonists (aminopterin, a-methopterin and amino-an-fol) have produced temporary remissions in only about 50 per cent of acute leukemias in children." The dosage schedule usually employed in the writer's cases of acute leukemia in children is 1 mg. of aminopterin intramuscularly daily for three to four days, followed by 0.5 mg. daily until there is conversion from a 'blast' type of bone marrow to a normal pattern, or nearly so. "An attempt is then made to maintain a normal blood and bone marrow by the oral or intramuscular administration of 2 to 5 mg. of methopterin daily. In a series of 10 cases of acute leukemias in children, 5 have died; the remainder have been maintained in a state of remission varying from 4 to 11 months. Aminopterin is a very potent and toxic folic acid inhibitor." Toxic effects noted in the writer's patients include severe leukopenia, severe depression and aplasia of the bone marrow associated with a severe anemia, leukopenia and thrombocytopenia in the peripheral blood, rectal bleeding, hematemesis, ulceration of the mucous membranes of the oral cavity and anus, loss of hair and hemorrhagic infiltration of the skin. "The bone marrow changes may be rapid, profound and irreversible. Fatalities have occurred for this reason. The margin of safety between a toxic reaction and death is at times very small. This is especially true in acute leukemia in adults. There is no evidence that folic acid antagonists cure leukemia. The use of the drug in chronic leukemia is limited by the early development of toxic phenomena."

Roentgen Ray Therapy.—"In spite of the fact that for many years roentgen therapy has been the method of choice there is considerable controversy as to the type of treatment to be used. Some radiologists prefer local treatment of the spleen, enlarged lymph nodes and the long bones. Recently the use of small doses of x-ray to the whole body has proved successful in treatment of chronic leukemia. Reactions are less likely to occur with the 'spray' technique. Total irradiation is not very effective in reducing a greatly enlarged spleen or marked adenopathy. In many instances the technique used will depend on the facilities available. During the first series of treatments it is wise to proceed cautiously, since there is considerable difference in the reactivity of patients to irradiation. Treatments can be given daily, two or three times weekly or less frequently. The white blood count and differential blood smear serve as a partial guide to the intensity and frequency of roentgen ray exposure. It is generally agreed that the improvement is manifested by reduction in size of the spleen or lymph nodes and increased red blood cell count.

"Symptoms of irradiation sickness include anorexia, nausea, vomiting and diarrhea. This reaction is more likely to occur when the upper abdomen has been treated. The intensity of the systemic reaction depends on the area of body surface treated, the portion of the body exposed and the dosage.

"Radioactive Phosphorous.—In chronic myelogenous leukemia, P^{32} is effective in producing clinical and hematologic remission. Following the use of P^{32} the leukocyte count decreases and the percentage of myeloblasts and myelocytes diminishes. The erythrocyte level increases in most cases. Clinically, asymptomatic improvement is noted with reduction in size of the spleen and lymph nodes. . . . It has been recommended that 1 to 2 millicuries be administered intravenously on the first day

and 0.5 to 1 millicuries on the third, sixth, tenth and fourteenth days. In patients with a high leukocyte count, it may be necessary to administer from 0.5 to 1.0 millicuries at weekly intervals until the white cells number approximately 30,000 per cu. mm. The use of large and concentrated doses may result in depression of erythropoiesis and platelet formation. Treatment with P^{32} does not produce radiation sickness or other subjective disturbances. . . . The possibility of radioactive phosphorous as a precipitating cause of an acute phase must be considered.

"It has been demonstrated that chronic lymphatic leukemia does not respond as favorably to therapy with P^{32} as the myeloid form of the disease. Smaller doses of P^{32} are required to reduce the total leukocyte count in lymphatic leukemia.

"General measures employed in the treatment of chronic leukemia include rest and an adequate diet. Restriction of activity is not necessary if weakness is not pronounced and the temperature is not elevated. Many of these patients are able to lead active and useful lives for many years. A high caloric diet, adequate in protein, is recommended. If the diet is well balanced, the need for supplementary vitamins is not great.

"Blood Transfusions. — Occasionally blood transfusions are required to correct the progressive anemia which develops during the course of the chronic leukemias. Since liver and iron are not effective in improving the anemia of leukemia, it is necessary to use whole blood when there is excessive weakness, restlessness, dyspnea and hemorrhagic tendencies. Symptomatic improvement may follow transfusions especially when the erythrocyte count is below 2,000,000 and the hemoglobin under 6 Gm. per 100 cc. It may be necessary to give three or more transfusions (500 cc.) to obtain the desired results."

Acute Leukemias.—"The course in most cases of acute leukemia is rapid, progressively downward, and usually fatal within three months. The treatment is essentially symptomatic with an attempt to make the patient comfortable. Because of the associated hemorrhagic tendencies, whole blood transfusions are of distinct value. Penicillin may be employed in controlling the secondary infection which is likely to accompany the ulcerative lesions in the oral cavity.

"Lymphoblastoma.—This group of diseases, the cause and nature of which are still unknown, include Hodgkin's disease, lymphosarcoma, reticulum cell sarcoma, lymphatic leukemia and mycosis fungoides. . . . Satisfactory treatment for the lymphomas has not been found. For localized lesions in Hodgkin's disease, roentgen irradiation is the treatment of choice. There is general agreement that for patients with disseminated lesions the use of nitrogen mustard therapy with roentgen irradiation of selected specific areas appears to be the most effective method. According to some observers, when a patient is first seen presenting only one group of nodes involved, better results are secured if that group is resected and roentgen irradiation is given to the area postoperatively and also to other nodes in the adjacent regions.

"The usual course of Hodgkin's disease, well managed by irradiation, is three to five years. In some instances it is shorter, while in the occasional case, palliation may be obtained for 10 years or even longer. There comes a time when irradiation no longer causes regression of nodes and improvement in general condition. In the past general deterioration and eventually fatality ensued in these patients. Nitrogen mustard, which appears to act similarly to roentgen therapy, has proved of great value in some of these cases. An occasional patient with Hodgkin's disease may again become sensitive to roentgen ray treatment following nitrogen mustard therapy. Nitrogen mustard is also recommended for patients with Hodgkin's disease in whom intensive roentgen ray therapy must be directed to the mediastinum, with consequent development of fibrosis of the lungs. This, of course, may be avoided by means of nitrogen mustard therapy. In general, the use of nitrogen mustard in Hodgkin's disease is indicated (1) when the lesions are generalized, (2) when the lesions, whether localized or generalized, are resistant to x-ray and (3) in the presence of generalized symptoms such as fever, itching and neurological manifestations which are particularly amenable to chemotherapy.

"Lymphosarcoma is best treated with roentgen rays. The response of giant follicular lymphoma to moderate doses of x-ray irradiation may be remarkable. All evidence of the disease may disappear and the patient may remain well for years. . . . The effect of nitrogen mustard in cases of generalized lymphosarcoma has been rather disappointing. Radioactive phosphorus, given intravenously in this disease as well as Hodgkin's disease, has produced disappointing results.

"Mycosis fungoides has been treated with both roentgen rays and nitrogen mustard without any remarkable effect on the final course of the disease.

"Polycythemia Vera.—Radioactive phosphorous is perhaps the most effective means of treating polycythemia vera and producing prolonged remissions in this disease. This material has the advantage of never producing nausea or vomiting or any other ill effects when administered in therapeutic doses. Radioactive phosphorous emits a beta ray, has a half life of 14.3 days and localizes in a large measure in bone marrow and blood-forming tissue. Radioactive phosphorous is usually administered as sodium acid phosphate and preferably intravenously since this eliminates the uncertainty of gastrointestinal absorption. From 3.5 to 7 millicuries is given initially. If at the end of from three to six months a hematologic and symptomatic remission has not been produced, a dose comparable to the initial dose or a fraction of it is given. When the symptoms are severe or the red blood cell count is so high that complications of thrombosis are feared, 500 cc. of blood are removed every other day until the hematocrit value has been reduced to approximately 40 per cent. Complete symptomatic and hematologic remissions of from six months to more than five years may be produced by this form of treatment. The complications of P^{32} are largely confined to severe leukopenia, thrombocytopenia and anemia resulting from overdosage or unusual sensitivity of the patient. It is well known that chronic leukemia, especially the myeloid type, occurs in about 10 per cent of all cases of polycythemia even though no irradiation or P^{32} is given. On the other hand, following P^{32} treatment, several patients with polycythemia vera have been reported terminating with acute leukemia.

"The nitrogen mustards produced hematologic and symptomatic remissions of from six months to two and a half years. A dose of 0.1 mg. per Kg. given on four consecutive days may produce symptomatic relief within three weeks after treatment. Hematologic values are within normal limits in some cases by two months after treatment. The toxic reactions that may result from the administration of the nitrogen mustards are nausea, vomiting, leukopenia and thrombocytopenia. The nitrogen mustards have the advantage of easy administration and do not require any elaborate setup. . . . Irradiation has been used in the treatment of this disease for many years. Spray irradiation, total irradiation or treatment of the entire body has been introduced in more recent years and is now regarded as effective and well tolerated. Remissions of from six months to five years have been reported by the method of total body irradiation.

"The use of arsenic (Fowler's solution) is a safe and reliable method of treating polycythemia. The serious objection to the use of Fowler's solution in polycythemia vera is; namely, the loss of appetite, nausea and vomiting which so commonly occurs. This is usually followed by loss of weight and disagreeable gastrointestinal symptoms which cause the patient to turn against the drug."

New Observations on the Treatment of Amebic Dysentery with Conessine — PLOYÉ, M. — *Revue du paludisme et de médecine tropicale*, 7: 211 (October 15) 1949.

There is increasing evidence that conessine is a weapon of the first order in the always difficult treatment of amebiasis, and that judiciously used it may supplement and even replace emetine which is often ineffective and always toxic. Conessine has sometimes been blamed for frequent excitation of the central nervous system, and for uncertain effects in acute amebic hepatitis. The latter reproach seems poorly founded on the basis of recent reports from France and Indo-China, and the effects on the nervous system can be avoided or at least attenuated with the avail-

able conessine preparations and with adjuvant treatment. Recent observation was made on the effect of conessine in children. The effect of conessine on dysenteric amebas in vitro was studied and it was found that it is at least as complex and poorly known as that of emetine. It has been said that the latter drug does not act as amebicide but as a vasoconstrictor; due to the vasoconstrictive action the congestive phenomena and the hemorrhages would regress and the amebas, no longer having erythrocytes at their disposal, would no longer be transformed into pathogenic forms but would persist in tetragenous forms. Apparently conessine does not act as an amebicide either. According to one writer the serum of a patient under conessine treatment inhibits cultures of amebas more intensely than that of a normal individual with addition of an equivalent amount of conessine. Like emetine, conessine possesses a direct toxic capacity against amebas although this capacity is lower than that of emetine; in the presence of a concentrated conessine solution (1:1,000 to 1:4,000) amebas become immobilized after a maximum of two and a half hours. Cultures of amebas are inhibited by conessine up to a concentration of 1:25,000 after a delay of four to five days, but this delay can be reduced to two days if the amebas are brusquely placed in contact with the conessine solution.

The following cases are reported by Porte from Saigon: The first case concerned a man, aged 30, with 10 to 15 mucosanguinolent bowel movements, who had received 0.16 Gm. of emetine before admission over a period of three days. The first attack of amebic dysentery had occurred seven months earlier and had been treated with 0.64 Gm. of emetine; relapses had occurred after two and four months and had been treated with emetine. The patient was in poor general condition, with asthenia, considerable loss of weight, dehydration, diffuse pigmentation of his face but not of the mucous membranes, and aphthoid ulcerous stomatitis. Conessine was given in a dose of 0.5 Gm. for four days, and then 0.3 Gm. and 0.2 Gm. for two days each, with a total dose of 3.0 Gm.; cortical extract, vitamins B_1 and C, and calcium were also given. Toxicity included disturbances of sleep, readily controlled by 25 mg. of phenergan, and a sensation of weakness and tremor, at first localized at the fingers but rapidly becoming generalized and causing reduction of dosage and early discontinuation of treatment. The bowel movements became normal within three days and the amebas disappeared from them. The general condition improved rapidly but the tenderness over the colon persisted. Because of the precachectic condition a second series of conessine treatment was started only after an interval of two weeks, again with a total dosage of 3.0 Gm. Insomnia was prevented by phenergan treatment, and rapid finger tremor was the only sign of toxicity but was well tolerated. The patient gained weight but his blood pressure remained low. The cecum was still moderately rigid, but not gurgling and not tender, and the left colon was spastic but not tender. Bowel movements were normal.

The second case concerned a man, aged 28, who had first developed acute amebic dysentery five months before admission, and had suffered relapses in spite of treatment with emetine, arsenicals, and iodine preparations. On admission he had 7 to 10 mucosanguinolent stools daily, and his general condition was poor. Conessine hydrobromide was given, in a dosage of 0.4 Gm. daily for five days, and then in a dosage of 0.3 Gm. with a total of 5.0 Gm. Toxicity included moderate weakness and slight tremor during the last days of treatment, subsiding spontaneously within a few days after its discontinuation; sleep was not disturbed. The pain subsided immediately, intestinal passage became normal after four days, appetite and strength increased rapidly, and the amebas disappeared after five days. As *Ascaris ova* were found santonin and calomel were given in large doses, without provoking a relapse of the dysentery. The colon was no longer tender but otherwise unchanged.

Thus in both cases emetine-resistant dysentery was rapidly sterilized by conessine while the intestinal lesions as such persisted; the antihistaminic phenergan controlled the insomnia readily but had no influence on the extremely annoying tremors and on the character changes which resembled those of chronic alcoholism and

which often appeared from the first day even in nonalcoholics.

Conessine cannot as yet be advised as preventive of amebiasis analogously to quinine in malaria. Valerian has been used successfully as sedative for insomnia and tremors caused by the drug. The new antiparkinsonian drugs have also been used and there is every indication that the nervous phenomena are of diencephalic origin. For reasons of safety the susceptibility of the patient should be tested by starting treatment with a dose of 2 to 3 instead of 5 tablets of 0.1 Gm. each.

The third case was one of presuppurative hepatitis, concerning a man, aged 37, who was admitted with high fever and moderate diarrhea without mucus or blood, of two days' standing. He had suffered first from acute amebic dysentery one and a half years earlier, had been treated with 0.72 Gm. of emetine, and had suffered a relapse after 10 months. Examination showed nothing abnormal at the level of the colon, but the liver extended 3 fingerbreadths below the costal margin, and was soft and tender. Rare hematophagic amebas were found in the stools. A total of 5.0 Gm. of conessine was given and was well tolerated, except for slight insomnia readily controlled by 25 to 50 mg. of phenergan in the evening, and for slight finger tremor. The results were spectacular with respect to general condition and temperature, and the hepatomegaly subsided within a week.

The fourth case also was one of presuppurative hepatitis, involving a man, aged 50, a native Annamese, with fever, hypochondriac pain, and mucous diarrhea of two days' standing. He had suffered from acute amebic dysentery two years earlier and had experienced frequent episodes of diarrhea since. Examination showed tenderness of cecum and colon, enlargement and extreme tenderness of the liver, and rare hematophagic amebas in the stools. Conessine was given in a daily dose of 0.3 Gm. for 13 days, and insomnia readily controlled by phenergan was the only reaction. The stools became normal and the parasites disappeared within two days, the temperature and the hepatic tenderness subsided after five days, and the hepatomegaly at the termination of treatment.

The fifth case was of the same type and showed a similar course.

The sixth case involved a girl, aged 3 and weighing 10.1 Kg., with 20 mucosan guinolent stools daily. The diarrhea hac first appeared five months earlier, and hac been treated with the common antidiar rheics and with emetine, but improvement had lasted only a few days. Cecum and sigmoid colon were spastic and tender liver and spleen were normal, and the stools contained hematophagic amebas. Conessine was given in a daily dose of 0.04 Gm for one week, and then in a dose of 0.02 Gm. with a total of 0.8 Gm. The number of stools did not definitely diminish until the end of the first week of treatment and they became normal after 12 days. The amebas disappeared after eight days. One month after termination of treatment functional cure was still maintained. The colon was still palpable but not tender. In this case the acute amebic dysentery had been present for five months and had not been controlled by emetine treatment which however had been poorly conducted.

Penicillin Therapy of Cardiovascular Syphilis — FLAUM, GERALD AND THOMAS, EVAN W. — *American Heart Journal,* 38: 361 (September) 1949.

In the experience of one of the writers, no harmful Herxheimer reactions during the treatment of cardiovascular syphilis have been noted in the past 12 years. "For this reason, perhaps, Herxheimer reactions were feared less than on other services where extreme caution has been urged in the treatment of patients with cardiovascular syphilis. Nevertheless, it was thought advisable, in patients who had not received previous antisyphilitic therapy, to start treatment with a preparation less rapidly spirocheticidal than penicillin." For this reason, the writers employed three injections of 0.2 Gm. of bismuth subsalicylate in oil, five days apart, before starting penicillin. "For a variety of reasons, however, not all patients received this preliminary treatment."

"The material in this report consists of the study of 39 patients with cardiovascular syphilis. Thirty had aortic insufficiency and 9 had saccular aneurysm or aneurysmal dilatation of the aorta."

"Of the 30 patients with syphilitic aortic insufficiency . . . . in addition to aortic in-

ufficiency, 8 patients also had aneurysmal ilatation of the aorta, 1 had saccular an- urysms of the arch of the aorta and of he innominate artery, and 4 were suspect- d of having coronary ostial stenosis." Twenty of the 30 patients gave a history f diminished cardiac reserve for periods f one month to five years prior to admis- ion, and 9 had had at least one bout of ongestive heart failure.

"Eight of the 30 patients had had no revious antisyphilitic treatment; only 3 f the remaining 22 had had as many as 0 injections of bismuth and 20 of arseni- al drugs."

"Three of the 8 patients who had had o previous antisyphilitic therapy received o preliminary treatment with bismuth. our of the remainder received three in- ections of 0.2 Gm. of bismuth subsalicyl- te in oil, and 1 received only two bis- nuth injections before penicillin was tarted.

"The 22 patients who had had some revious antisyphilitic treatment were not iven preliminary bismuth, although some ad received no antisyphilitic therapy for everal years.

"Penicillin was given in full dosage from he start of treatment (30,000 to 50,000 nits every three hours). Total dosage was to 6 million units. Three patients receiv- d penicillin in oil and beeswax (300,000 o 600,000 units daily), totaling 4.2, 7.2 nd 9.0 million units, respectively."

"There were no untoward reactions ttributable to penicillin therapy in any f these patients. Three presented cardiac ymptoms during treatment. One of the 3 had been admitted in congestive heart ailure with a history of precordial pain nd paroxysmal dyspnea, and he had had wo bouts of heart failure in the year prior o admission. After treatment for conges- ive heart failure, penicillin was started vithout preliminary bismuth. During the irst week of treatment the patient ex- erienced several bouts of precordial pain o different from his previous attacks; luring the second week of penicillin he xperienced no untoward symptoms. He lied in his fourth bout of congestive heart ailure two months after the completion f penicillin treatment. The second of these patients was admitted in congestive heart ailure with a history of precordial pain and paroxysmal dyspnea for an unde- termined period before admission. She did not respond to the usual measures for congestive heart failure, and penicillin was started after she had received three injec- tions of bismuth. She remained in conges- tive heart failure and died five weeks after penicillin therapy. Neither of these pa- tients had had previous antisyphilitic ther- apy. It was considered that the natural course of the disease prevailed in these 2 patients.

"A third patient gave a history of di- minished cardiac reserve for two years prior to admission. He had had 'several' bouts of congestive heart failure during this time, with precordial pain and noctur- nal paroxysmal dyspnea, and had been on digitalis for one year. He experienced symptoms during penicillin therapy similar to his previous attacks. When seen two months after treatment, he stated that he had not had nocturnal paroxysmal dyspnea, and he was fairly well compensated.

"There were no untoward symptoms during or after penicillin therapy in the remaining 27 patients."

"Four patients with saccular aneurysm and 5 with diffuse aneurysmal dilatation of the aorta were treated with penicillin. Only 1 patient had symptoms referable to the aneurysm. In this patient, pressure on the left main bronchus had produced sec- ondary pulmonary changes, and he has since died.

"Three patients had had large amounts of previous antisyphilitic treatment with heavy metals and arsenical drugs. Three had had no previous treatment; they did not receive preliminary treatment with bis- muth. No reaction of any kind was noted in the penicillin treatment of these pa- tients. With the exception of the 1 patient who died, all were asymptomatic when last seen."

As for clinical improvement following penicillin therapy, 7 of the patients with aortic insufficiency "claim to be improved" after treatment. "Of these 7 patients, 1 denied symptoms of diminished cardiac reserve on admission but later said he had had dyspnea on exertion; 3 described dyspnea on exertion (1 with precordial pain); 1 described dyspnea on exertion and nocturnal paroxysmal dyspnea; and 2 had been in congestive heart failure,

with histories of precordial pain and nocturnal paroxysmal dyspnea. The last 2 patients were on digitalis at the time of treatment and have continued it since. All 7 patients are working at present, and claim to be able to do more work with less discomfort than formerly. Adequate antisyphilitic therapy is expected to arrest a syphilitic inflammatory process in the aorta, but it is difficult to attribute an increase in cardiac reserve to the arrest of such a process." The writers believe that the apparent improvement in cardiac reserve noted by these patients is due to a general systemic improvement following the eradication of the chronic low grade syphilitic infection.

In conclusion, it is believed that the danger of Herxheimer reactions has been overemphasized, but until much larger series of patients have been observed, it is advisable to administer bismuth before starting penicillin in patients who have received no previous antisyphilitic therapy.

The Treatment of Pneumococcic Meningitis with Penicillin. A Study of 125 Consecutive Cases, with 73 Per Cent Recovery—APPELBAUM, EMANUEL, NELSON, JACK AND ALBIN, MICHAEL B. — *American Journal of the Medical Sciences,* 218: 260 (September) 1949.

The writers treated 125 cases of pneumococcic meningitis with penicillin from June 13, 1944, to October 20, 1948. "The diagnosis was definitely established in each instance by culturing or typing the organism from the spinal fluid.

"Clinical Aspects.—Most of the patients presented the typical picture of meningitis on admission. The individual patients showed considerable variation in the severity of the disease, but most of them appeared critically ill.

"There was a wide range in age. (See table 1.)

"In this series of cases a primary focus was established in 78 instances. A definite focus in the ear, mastoid or both was found in 36 of the cases. While this series shows a record of only 6 instances of definite sinusitis, it is possible that this condition existed more frequently than it was recognized. In 27 patients the presence of

Table 1. Recoveries in Relation to Age

Age Years	Number of Cases	Number of Recoveries	Number Deaths
	Number of Recoveries and Deaths in Each Group		
Under 1	28	22	6
1 to 10	16	15	1
11 to 20	7	7	0
21 to 30	14	13	1
31 to 40	9	7	2
41 to 50	23	19	4
51 to 60	17	8	9
61 to 70	8	0	8
71 to 80	2	1	1
81 to 90	1	0	1
Total	125	92	33

pneumonia was regarded as the probab primary focus. There were 7 cases of hea injury with a fracture through a sinu mastoid or base of the skull in 5 instance In 2 cases the meningitis followed cell litis of the face. There remained 47 cas in which the meningitis was preced either by no obvious illness or by a simp upper respiratory infection.

"Bacteriologic Diagnosis. — Diagnost lumbar punctures were performed in a the cases on admission. The cerebrospin fluid showed varying degrees of turbidit The cells were greatly increased in numb with polymorphonuclears predominatin In the majority of instances the prote content was moderately to greatly increa ed. Sugar was either absent or considerab diminished in all cases. Stained smears the cerebrospinal fluid showed varyin numbers of gram-positive diplococci in 1 instances. Pneumococci were grown fro the fluid in 120 of the cases. The orga isms were typed in these cases from th cultures and in many instances direct from the spinal fluid. In the 5 cases wit negative cultures, the pneumococcus w identified by direct typing from the spin fluid.

"Many strains of pneumococci we represented in the series. There was an a parent relationship between meningitis du to type 3 and an otitic infection as show by the fact that of 15 cases due to th type, the primary focus was otogenic in 1 instances. Blood cultures were made in 6 cases prior to the institution of sulfon mide and penicillin therapy. These we positive in 28 instances.

"Penicillin sensitivity determinations ere made on 75 strains. The range of ensitivity of the organisms is shown in able 2. The marked susceptibility of these rganisms to penicillin is quite apparent.

"Treatment.—In this series penicillin as administered intrathecally in all but instances. In addition, all the patients ere treated with penicillin intramuscularly nd most of them received also a sulfona- ide, usually sulfadiazine. There was con- iderable variation in the intrathecal and ntramuscular dosages of penicillin as well s in the number of intraspinal injections nd the duration of intramuscular treat- ent. The schedule of penicillin therapy nally evolved is shown in table 3.

"In 8 cases an attempt was made to reat the patient with penicillin given intra- nuscularly but not intraspinally. In ad- ition these patients received sulfadiazine. A satisfactory response was obtained in nly 2 of these cases. In the remaining 6 nstances there was a failure of response equiring the additional use of intrathecal enicillin. . . . In 10 instances mastoidec- omy was performed.

"Results.—In this series of 125 cases here were 92 recoveries and 33 deaths, a ecovery rate of 73 per cent. . . . The prog- osis was decidedly worse in the older age roups. . . . Among the fatalities there were 7 cases in which adverse contributory factors were present. These included 3 instances with inadequate intraspinal penicillin therapy, 2 cases complicated by a secondary *B. pyocyaneus* meningitis, a case with acute bacterial endocarditis, and a case associated with multiple severe injuries. In addition, 5 of the patients died within 24 hours following the institution of penicillin therapy.

"Spinal Fluid Changes During the Course of Treatment.—With the institution of penicillin therapy a fairly prompt disappearance of the pneumococci was noted in the vast majority of the cases. . . . The early disappearance of the organisms could not be relied upon as an indication of the control of the infection. A more dependable index is the return of the sugar to normal.

"Repeated determinations of the concentration of penicillin in the spinal fluid were made in 94 instances. These showed enormous variations and could not be correlated with the clinical results.

"Complications and Reactions Due to Intrathecal Penicillin.—In this series of cases a reaction attributable to the intrathecal administration of penicillin was encountered in several instances. . . . Arachnoiditis followed by subarachnoid block occurred in only 1 instance, and irritative cerebral phenomena were encountered in 4 cases. The outstanding irritative symptoms consisted of pyrexia, delirium and convulsions which occurred within a few hours after the intrathecal injection of the drug. . . . This type of reaction was induced in 3 instances by dosages of 50,000 to 100,000 units of the drug and, in 1 instance, by an inadvertent injection of 500,000 units. Following the subsidence of the reaction, 2 of the patients were able to tolerate smaller doses of penicillin intra-

Table 2. Penicillin Sensitivity of Pneumococci—75 Strains.

Range of Sensitivity Units Penicillin per ml.	Number of Strains
Under 0.001	0
0.001-0.004	33
0.005-0.016	39
0.02-0.06	3
Over 0.06	0
Total	75

Table 3. Penicillin Dosage Schedule in Pneumococcic Meningitis.

	Intrathecal		Intramuscular	
	Units per Injection	Injections	Units Per Day	Days of Treatment
Age Up to 4 years	25000-50000	3-5	400,000	7-10
Older Children and Adults	50000-100000	3-5	800,000	7-10

spinally without untoward effect. With regard to the fatalities . . . . in the case with subarachnoid block the death was unrelated to the reaction while in the other instance the fatal issue appeared to be closely related to the reaction.

"In addition there were 4 instances of a secondary meningitis due to *B. pyocyaneus* introduced during the intrathecal administration of penicillin."

Relapses.—Relapse occurred in only 3 instances, in 2 of which intraspinal penicillin had not been used prior to the relapse. "Following a short course of adequate intraspinal penicillin therapy these 3 patients recovered completely.

"Sequelae.—In this series there were 4 instances of serious damage to the brain resulting in hydrocephalus, mental impairment or paralysis. These were all in infants under 1 year of age. In 1 of these, a 3 month old infant, spinal block was present before treatment was begun, necessitating intraventricular therapy. There were also 4 cases of deafness partial or complete."

Treatment of Auricular Flutter with Digitalis—Bloomfield, Arthur L. —*American Journal of Medicine*, 7: 437 (October) 1949.

"The use of digitalis in auricular fibrillation has been clearly defined on a rational basis for many years. Every doctor is familiar with the principle of slowing the ventricle by means of this drug, and all agree on the need of maintaining a slow ventricular rate by adequate continuous dosage. . . . . It is confusing, therefore, to find in most discussions of the treatment of auricular flutter—a condition so closely related to fibrillation—an entirely different prescription for the use of digitalis. It is the fact that this prescription, obviously obsolete, is still given in some widely used recent textbooks which prompts the following remarks.

"The procedure, as described, is essentially as follows: Digitalis is given in large doses until the ventricle is slowed just as in cases of fibrillation. The drug is continued up to the point of tolerance, whereupon within a few days flutter may be expected to pass over to fibrillation. But now instead of continuing digitalis the drug is stopped altogether, whereupon a normal mechanism is said often to supervene within a few hours or days. It should be emphasized that the crucial point in the prescription is the stopping of digitalis as soon as fibrillation comes on; it is implied that continued administration of the drug at this point may prevent the return of a normal mechanism. Inasmuch as the prescription is so directly at variance with the established usage of digitalis in auricular fibrillation, one must examine the results which have been obtained with it as well as its theoretic validity."

"It is of interest that the 8 cases upon which the classical therapy is based do not really seem to give it strong support. First, flutter does not go over to fibrillation with any regularity. In the 8 cases it failed altogether to fibrillate and in a fourth digitalis was given for a year before fibrillation supervened. In 2 more cases normal rhythm was not restored when digitalis was withdrawn. In only 3 of the 8 cases did the prescribed sequence of events really unfold itself, and in these the interval between cessation of digitalis and resumption of normal mechanism varied greatly."

Ritchie points out that it worked in about only one half of his cases and that even then there was likely to be a return to flutter or to fibrillation. "He raises the question of whether just enough digitalis to control the ventricular rate may not be better therapy than the large doses which are supposed to induce fibrillation.

The writer's experience gives no support to the theory or practice of the classical therapy. He has seen patients with auricular flutter revert to a normal mechanism without any digitalis and with or without a recognized intervening period of fibrillation. "Some patients have gone back to normal mechanism while on digitalis.

"Flutter should therefore be treated with digitalis on the same basis as fibrillation. Should flutter go over to fibrillation the drug should not be stopped but continued in order to keep the ventricle slow just as in any instance of auricular fibrillation. There is no formula whereby return of normal mechanism can be regularly induced by the use of digitalis, and quinidine should be used if prompt restoration is to be attempted."

The Rh Factor — KING, E. L.—*Surgery, Gynecology and Obstetrics*, 89: 362 (September) 1949.

"The Rh factor is really a complex, composed of the subgroups Rh_0, Rh′, and Rh″. Eighty-five per cent of Caucasians possess the Rh_0 factor along with one or both the others; about 3½ per cent possess only one factor, and about 13 per cent lack all 3 factors. The latter are the true Rh negative persons, though this term is universally applied to those lacking the Rh_0 factor."

"The Rh factor acts as an antigen and may stimulate the production of antibodies if introduced into the blood of an Rh negative individual. This may be accomplished by blood transfusion or by pregnancy produced in an Rh negative woman by an Rh positive man. Here the red blood cells evidently pass from fetus to mother through microscopic lesions in the placenta, probably seeping through all during the pregnancy. Some contend, however, that this transfer occurs most often during labor. At any rate, it appears that in pregnancy the process of antibody formation is a gradual one, so that in the first pregnancy they cannot be detected. Once the antibodies are formed, they may cross the placental barrier from mother to child in a subsequent pregnancy and attack the red cells carrying the Rh factor, thus producing hemolytic disease. Three types can be differentiated clinically; the hydropic (mortality, nearly 100 per cent), the icteric (40 to 50 per cent fatal), and the anemic (with a risk of 15 to 20 per cent). The infant may die in the uterus days or weeks before delivery, may die shortly after birth, or may survive, especially when promptly and properly treated. Once sensitization of a woman is established, it persists throughout life, and if she has lost a child from hemolytic disease, all subsequent Rh positive children borne by her will suffer the same fate. However, this mother-to-child antibody transfer does not always occur, or it may be so slight as to be of no consequence. Furthermore, about 50 per cent of such women are not capable of sensitization.

"These antibodies may be of the type that cause agglutination of the red cells in saline, or they may be of the 'blocking' or 'incomplete' variety which prevent or 'block' the agglutinating property of the first type because of their greater affinity for the combining units on the red cells. They agglutinate Rh positive cells in a protein medium. They result from more prolonged immunization, and may ultimately replace the simple antibodies, hence their presence, especially if found alone and in high titer, establishes a more serious (but by no means is this infallible) prognosis for the present, or any future infant. If one or both antibodies are found persisting in the maternal blood months or years after delivery, the outlook in a future pregnancy is especially somber.

"Of the 15 per 100 females who are Rh negative, some are not in the childbearing age, some are not married, and a few are married to Rh negative men. Hence only about 9 per cent of all pregnancies occur in Rh negative women married to Rh positive men, and . . . . many of these women are not susceptible of sensitization. Furthermore, about 58 per cent of Rh positive men are heterozygous for the Rh factor, hence that percentage of their children should be Rh negative. Thus, only in about 1 to 350 (some say 1 to 500) deliveries will the child be affected in varying degree with hemolytic disease of the newborn. This will not occur in the first term pregnancy unless the mother has been sensitized by blood transfusion or by a pregnancy which has progressed to 4 or 5 months or more before abortion occurred. The disease is most often noted in the second or third and subsequent pregnancies, rarely not until the fifth or sixth." In 569 consecutive patients in the writer's practice, his group found 98 of the women to be Rh negative. "Of these, the potentiality of Rh sensitization was present in 43. In 24 women it did not develop, in 10 it was found, 8 were still undelivered, and in 1 the outcome was not known. Of the 10 women, 6 lost a total of 8 babies. Thus, 1.05 per cent of these 569 women lost their babies from hemolytic disease. This is much higher than the ratio usually given.

"Three Hr factors, the reciprocals of the corresponding Rh factors, have been found. Of these, only the Hr′ is capable of producing antibodies, and that very rarely."

Once sensitization is established, it is permanent. The recent work with the haptens offers great promise of combating this. "At present, 15 to 30 liters of blood must be processed to secure enough haptens to desensitize one patient." One writer has suggested the use of methionine, 5 Gm. daily, throughout pregnancy for its protective influence on the fetal liver, the organ chiefly affected. This may be of value.

"As far as transfusion is concerned, the clinical implication is clear. Rh typing should be routine, and no Rh negative person, male or female, should receive Rh positive blood. If this has been done, either in the days before the Rh factor was known, or in case of great urgency, that patient should under no circumstances be transfused again with Rh positive blood. The risk of a fatal reaction would be too great.

"In obstetrical practice the Rh type of every pregnant woman should be determined early. If she is Rh negative and has had a transfusion, the Rh type of the transfused blood should be ascertained if possible. Also, the Rh status of her husband and of other children (if any) should be determined. If she is a multigravida, or if she is a primigravida with a history of transfusion, tests for antibodies should be done at monthly intervals after the fifth month, and if present, titers should be noted. In such a case the prognosis for the child should be guarded, especially if the titer is rising; a rising titer of blocking antibodies is considered particularly grave."

The termination of pregnancy 3 or 4 weeks before term by cesarean section or by induction of labor has not given satisfactory results in the writer's hands, or in the experience of others. "The babies are either severely damaged already, or they are in good condition. In either instance, the hazard of prematurity is an added risk.

"After delivery, the Rh type of the baby and a study of its blood should be performed at once. If the baby is Rh positive, and is jaundiced or anemic with an abnormally high percentage of erythroblasts, transfusion with Rh negative blood should be performed at once. The same is true if the baby is Rh negative, and the clinical picture is that of hemolytic disease. In such a case, the true Rh type may be masked by the presence of antibodies, or the trouble may be caused by another type of sensitization. If the baby appears normal, it should be very closely observed clinically, and with hourly blood studies, and transfused as soon as any abnormal developments are noted." The writer prefers the replacement transfusion, using the umbilical vein if done soon after birth, the femoral if done later. "The long plastic catheters of Diamond are employed, injecting 30 cc. at a time, then withdrawing 30 cc., injecting and withdrawing again, and continuing this until 350 to 500 cc. of blood have been used." The writer considers this preferable to the use of repeated small transfusions; however, these have been used successfully in many cases.

"It is important to discuss the situation frankly with the parents. One should not be overly optimistic or unduly pessimistic."

A Case of Typhoid Fever Treated with Chloromycetin — MELFI, JOSÉ — *La prensa médica argentina*, 36: 1737 (September 2) 1949.

The author reports the case of a youth, aged 19, who came to his office complaining of headache, sore throat, dry cough, constipation and generalized pain; his temperature was 38° C., his pulse rate was 90, and he showed tonsillitis, a dry saburral tongue and signs of bronchitis. Local treatment of the sore throat, and sulfadiazine treatment were instituted; after two days the patient returned with an unchanged syndrome except for the fact that diarrhea had supervened. Six days later the patient was reported to be afebrile but in a condition of intense prostration so that he had to be seen in his home. Examination showed a temperature of 39.7° C., a dicrotic pulse with a frequency of 110, extreme adynamia, a stuporous facial expression, slight subicterus of the conjunctivas, dry lips, a dry saburral edematous tongue, slight ulceration of the velum palatinum (Daguet's ulceration), reddened tonsils, signs of bronchitis, normal heart sounds, meteorism, lenticular efflorescences of the abdominal skin, and some at the level of the lower portion of the thorax, enlargement of the liver to 1 fingerbreadth below

the costal margin with a smooth slightly tender border, and splenic enlargement to percussion although the spleen was not palpable. The right iliac fossa showed gurgling but no tenderness. Headache was present and was accentuated by movements of the head. There was mental obnubilation, marked insomnia, lack of appetite, intense thirst, diarrhea and scanty diuresis. A diagnosis of typhoid fever was made and the Widal reaction was found positive in a dilution of 1:500 for the somatic antigen and 1:200 for the ciliary antigen, while it was negative for paratyphoid fever. Chloromycetin treatment was instituted 11 days after onset of the syndrome. The patient weighed about 55 Kg. and was given 0.25 Gm. of the drug at intervals of two hours; the temperature fell gradually and became normal within four days. The dosage was then decreased to 0.25 Gm. at intervals of four hours; the total dosage amounted to 21 Gm. The pulse rate fell from 110 to 68 over a period of one week. The mental condition improved with the defervescence, and bronchitis, rash and adynamia subsided one week after institution of treatment; headache and diarrhea subsided after four days while the anorexia persisted.

Chloromycetin is well tolerated without secondary reactions and easily administered by mouth; it is rapidly effective. The dosage in typhoid fever should be 50 mg. per Kg. daily.

Streptomycin Therapy of Tuberculous Pneumonia in Negro Adults — KIRBY, WILLIAM M. M., SIMPSON, ROBERT M. AND CREGER, WILLIAM P.— *American Review of Tuberculosis*, 60: 343 (September) 1949.

"The present report is a description of the results obtained in the 15 Negro adults with tuberculous pneumonia who were treated with streptomycin on the Stanford Service of the San Francisco Hospital from 1946 to 1949."

"The Negro adults included in this study varied in age from 18 to 45; 8 were women, and 7 men. All were hospitalized during streptomycin therapy and were kept on bed rest except for bathroom privileges. Because of the serious nature of the illness, the patients remained in the hospital for considerable periods following cessation of antimicrobial therapy. Streptomycin was administered for two to four months in doses of 1.0 Gm. daily, which was usually given in two injections at 12 hour intervals. Other measures, including various forms of collapse therapy and other surgical procedures, were performed as they seemed indicated before, during, or after streptomycin therapy.

"The diagnosis of tuberculous pneumonia was made on the basis of extensive, confluent, exudative pulmonary disease in patients manifesting considerable fever and toxicity. Posthemoptoic infiltrations, which cleared rapidly and were presumably caused by the aspiration of blood, were not included."

"Group 1.—Patients in Whom There Was Improvement, Followed by Relapse: In 11 of the 15 patients, there was an initial period of improvement, followed by relapse. . . . Four of these patients are dead, and it is likely that most if not all of the remaining 7 will eventually succumb to the disease."

A typical example of the course of events occurring in this group was a 23 year old colored housewife who had been acutely ill with tuberculous pneumonia for two months prior to the administration of streptomycin. "Symptomatic improvement was noted within a few days after starting therapy, and within two weeks the temperature, which had been rising to 102° F. daily, gradually returned to normal. During the two months of streptomycin therapy she gained 10 pounds and her cough and sputum were greatly diminished. At the end of the treatment period, however, the sputum remained positive for tubercle bacilli and the organisms cultured were highly resistant to streptomycin. Because of the presence of cavitation in the left first interspace, a thoracoplasty was scheduled. Within two weeks after discontinuing streptomycin, however, her temperature again became elevated and her condition deteriorated so rapidly that the operation was never performed. Streptomycin was again started, but within five days she became almost totally deaf and the drug was discontinued. She died four months after completion of the first course of streptomycin therapy."

A 45 year old, colored male had had cough, fever, and left chest pain for one month, during which he lost 30 pounds. "During a three month course of streptomycin therapy he became afebrile and gained 15 pounds. Thoracoplasty was scheduled, but within two weeks after cessation of streptomycin his fever returned and he began to lose weight. Tubercle bacilli obtained at this time grew in the presence of 10 γ per cc. of streptomycin, but were inhibited by 100 γ. Streptomycin was given for a second two month course, but his condition grew steadily worse and he died two months after completion of the second course."

A 27 year old, colored male was thought to have a nontuberculous bacterial pneumonia in October 1946 on the basis of cough, sputum, right chest pain, and right upper lobe infiltration on the roentgenogram. "He was treated by a private physician but failed to improve, and in April 1947 he was admitted to a nearby sanatorium with tuberculous pneumonia. He had lost 25 pounds and was very ill. Pneumoperitoneum was instituted and he received streptomycin for 11 weeks from July to September 1947. During this period he showed marked symptomatic improvement and gained 5 pounds, but his condition became worse almost immediately after antimicrobial therapy was discontinued. He was transferred to the San Francisco Hospital in January 1948 where pneumoperitoneum was continued, but the situation was obviously hopeless and the patient died four months later.

"The course in the other 8 patients in this group was strikingly similar to that which occurred in these 3 patients. In 5, some form of collapse therapy was administered, but in every instance it was inadequate to control the disease. Three patients received both pneumothorax and pneumoperitoneum. One patient received a 2 stage thoracoplasty, but the cavities were not closed by this procedure and she is steadily getting worse.

"Group 2.—Patients Showing Improvement, Without Relapse: In contrast to the 11 patients in group 1, the results in the 4 patients comprising group 2 have been highly satisfactory to date. Since the objective of this study is to discover factors which are of importance in bringing about a favorable therapeutic result, these 4 cases will be presented briefly. Two received pneumoperitoneum in addition to streptomycin, and 2 had pneumonectomies.

"One of the most striking responses occurred in a 26 year old male. . . . He had been ill for 10 weeks prior to streptomycin therapy, with cough, sputum, fever, abdominal cramps, and diarrhea. His temperature, which was 104° F., fell to normal during the first month of treatment, the gastrointestinal complaints disappeared, and he gained 30 pounds. Pneumoperitoneum was started two weeks after completion of the 90 day course of streptomycin. Sputum and gastric cultures have been negative for tubercle bacilli since the second month of streptomycin therapy. In view of the sudden onset, the bilaterally symmetrical chest lesions, the gastrointestinal lesions, the prompt 'conversion' of the sputum, and the lack of definite cavitation, it is possible that the disease in this case may have been hematogenous in origin. If so, the predominately interstitial character of the lesions may account in large part for the favorable response obtained.

"The other patient who received pneumoperitoneum was a 22 year old housewife with a left lower lobe pneumonia which showed considerable progression during the first five weeks in the hospital, before streptomycin was administered. . . . Streptomycin was given in daily doses of 1.0 Gm. for 90 days, and two weeks later pneumoperitoneum was instituted. She gained 20 pounds and sputum and gastric washings became negative for tubercle bacilli during the second month of streptomycin therapy. Six months following the completion of antimicrobial therapy, she is showing continued improvement, and the plan is to continue pneumoperitoneum for several years.

"Two patients have recently been observed in whom a more aggressive approach seemed indicated. The first of these was an 18 year old housewife who was three months pregnant when she entered the hospital in September 1948, with an extensive tuberculous pneumonia of the left lung. Although she had a daily temperature elevation of 102° F. or higher and had lost 15 pounds, she showed a surprising lack of awareness of her symptoms. She was placed

on streptomycin September 30, 1948, and two days later the pregnancy was interrupted by abdominal hysterotomy. There was a weight gain of 13 pounds during three months of streptomycin therapy, but at the end of treatment she still had a daily fever of 99.5° F. Realizing that her course without further treatment would be like that of the cases in group 1, a second course of streptomycin was started January 19, 1949, and left pneumonectomy was performed January 29, 1949. The postoperative course was uncomplicated. At present, two months after the operation, she is afebrile, her sputum and gastric washings are negative for tubercle bacilli on smear and culture, and she is gaining weight. She refuses thoracoplasty, but a permanent left phrenic interruption is scheduled. The follow-up period is too short to predict the eventual outcome, but the outlook so far is certainly favorable as compared with the first 11 patients. It is of particular interest that a sensitivity test started before the pneumonectomy, but reported a month after the operation, showed the organisms to be resistant to 1,000 γ of streptomycin per cubic centimeters of medium.

"The second case was a 39 year old housewife who was found to have a tuberculous cavity of the right upper lobe in late 1947. By May of 1948, despite right pneumothorax and pneumoperitoneum, the cavity was still open and it contained a fluid level. On May 15, 1948, the cavity contents suddenly flowed into the right lung, causing an extensive spread of the disease. During the next six months she lost 35 pounds and ran a downhill, febrile course. Because her condition was considered desperate, streptomycin therapy was started December 16, 1948, and a right pneumonectomy was performed January 8, 1949. The postoperative course was stormy for two weeks, but since then she has been afebrile and two months after the operation has gained 5 pounds. Several sputum smears and gastric cultures, since surgery, have been negative for tubercle bacilli. She refuses thoracoplasty. Again, the follow-up period is very brief, but the situation seems encouraging and the condition certainly would have terminated fatally without surgery."

Biologic Complications of Penicillin Therapy — Sommer, Leonard S. and Favour, Cutting B. — *American Journal of Medicine*, 7: 511 (October) 1949.

Four case histories are presented which demonstrate clearly the importance of following shifts in bacterial flora of certain patients during penicillin therapy.

"Case 1.—M. D., a 68 year old white female, entered the hospital on August 27, 1946, because of persistent vomiting, periumbilical pain and weight loss of three weeks' duration. A posterior gastroenterostomy had been performed in 1931 for a poorly controlled gastric ulcer. She had been well until postprandial epigastric pain recurred in 1945, at which time a gastrojejunal ulcer was demonstrated by x-ray. Three weeks before admission weight loss, anorexia, pain and vomiting recurred. The remainder of the past history was noncontributory.

"Physical examination revealed a poorly nourished elderly woman complaining of abdominal discomfort. Temperature was 98° F., pulse 112, respirations 22 and blood pressure 120/75 mm. Hg. The chest was moderately emphysematous and hyperresonant to percussion. Examination of the lungs and heart was otherwise unremarkable. The abdomen showed only direct periumbilical tenderness. The remainder of the examination was negative.

"The blood Hinton test was negative. Examination of the urine and the stool guaiac test were negative. On admission hemoglobin was 11 Gm. per cent, hematocrit 34 per cent, white blood cell count 8,500 with a normal differential. Blood chemical values were not remarkable. A gastrointestinal series revealed a jejunal ulcer. Electrocardiogram showed premature auricular contractions.

"On a Sippy II diet, high protein drinks and intravenous fluids the patient improved but symptoms persisted and the nightly gastric residue was 500 cc. On the sixteenth hospital day prophylactic penicillin, 40,000 units every four hours intramuscularly, was started and a subtotal gastric resection with a Polya type anastomosis was performed. The immediate postoperative course was satisfactory. On the second postoperative day the patient's

temperature rose to 103° F. and the patient became cyanotic. The trachea and heart were shifted to the left and there was dulness at the left base. The white cell count was 1,150 per cu. mm. with 32 per cent polymorphonuclear leukocytes. An electrocardiogram showed sinus tachycardia. In spite of oxygen, morphine, heparin and penicillin the patient remained in semishock for 12 hours and then expired.

"Postmortem examination performed three hours after death revealed a confluent bronchopneumonia of the lower two thirds of the left lung with a small left hydrothorax. The lung had the consistency of soft liver. Five microscopic sections showed an acute cellular reaction and many bacilli, both free and within phagocytes. Multiple cultures of the involved pulmonary tissue yielded a pure growth of *Bacterium coli*. No other pathologic cause for death was found."

"Case 2.—H. K., a 67 year old white male, was admitted to the hospital on December 14, 1946, with a diagnosis of carcinoma of the stomach. During the previous eight months the patient had had continuous epigastric pain associated with anorexia, constipation and a weight loss of 30 pounds. The diagnosis of gastric cancer had been made but because of an unexplained anemia and leukopenia operation had been delayed. Three days before admission the patient became completely obstructed. The past history was noncontributory.

"On entry the temperature was 99.4° F., pulse 90, respirations 20 and blood pressure 112/55 mm. Hg. The patient was an emaciated, chronically ill, dehydrated elderly man. A few rales were heard at the left base of the lung. The heart was slightly enlarged to the left. The abdomen gave a sensation of fulness in the epigastrium but no mass was felt. The rectum contained impacted feces. The remainder of the examination was not significant.

"The blood Hinton test was negative. Urine showed 1+ protein and 5 to 10 white blood cells per high power field. Hemoglobin was 10.2 Gm. per cent, white blood cell count 1,800 with 20 per cent neutrophils and 80 per cent lymphocytes. Blood urea nitrogen was 26 mg. per cent and the serum total protein 5.7 Gm. per cent.

"The patient was placed on intermittent Wangensteen suction, high protein drinks and was given parenteral fluid and vitamin therapy. With prophylactic sulfadiazine, 2.5 Gm. daily, and penicillin, 50,000 units intramuscularly every three hours beginning immediately before operation, a subtotal gastrectomy was performed on the fifth hospital day and the tumor was removed from its adherence to the pancreas. The early postoperative course was uneventful but the next day the patient had a shaking chill and the temperature rose to 104° F. There were numerous moist rales in both lungs and a chest x-ray was consistent with a widespread peribronchial pneumonia which was more widespread on the right than on the left. The white blood cell count was 1,900 per cu. mm. The urine was clear. Sulfadiazine was discontinued and penicillin was increased to 50,000 units every two hours. At no time did the patient vomit. His condition deteriorated in spite of oxygen and blood transfusions. Shock supervened and the patient expired on the eighth hospital day.

"At the autopsy performed four and one-half hours post mortem the cause of death was found to be marked bronchopneumonia involving all lobes of both lungs; it was interpreted as resulting from aspirated material. Four stained microscopic sections showed the alveoli to be filled with huge numbers of gram-positive and gram-negative bacteria, with a sparse cellular reaction. Three specimens of lung tissue grew *Proteus vulgaris* in pure culture and a fourth, *Pseudomonas aeruginosa*. There was no evidence of metastatic disease and the operative site was intact."

"Case 3.—C. P., a 69 year old, white, retired toolkeeper was admitted to the hospital on October 19, 1947, because of fever, cough and dyspnea. During the previous 10 years the patient had had a chronic productive cough without hemoptysis and had had four bouts of bronchopneumonia. He had drunk alcohol heavily for years. For three years he had been maintained on digitalis with fair cardiac compensation. For two years the patient had not been working. Six days before admission he noted an increase in his cough. On the

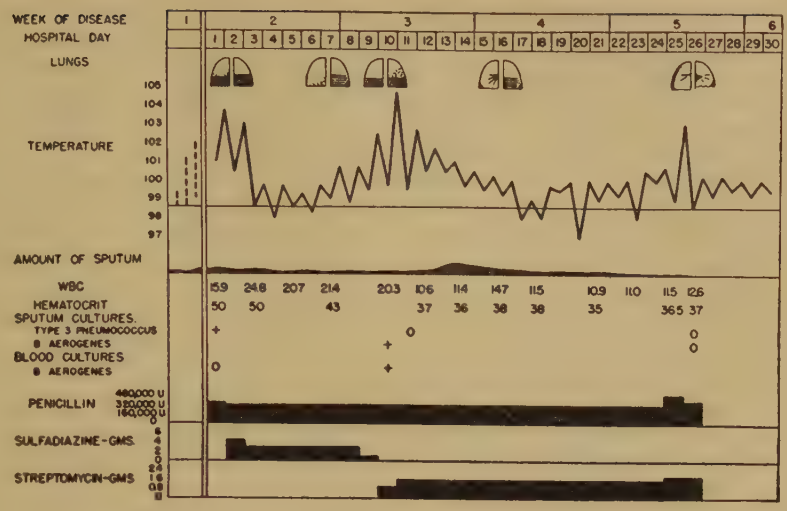

Fig. 1. Hospital course of Case 3 (C. P.). Note the gradual elevation in temperature to a high spike with chill on the tenth hospital day, concomitant with the recovery of pure cultures of *Bact. aerogenes* in sputum and blood.

day before admission he developed a fever of 102° F. and became delirious.

"Physical examination on admission revealed an acutely ill, moderately well oriented man, dyspneic, slightly cyanotic and dehydrated. The temperature was 103° F. by rectum, pulse 126 and regular, respirations 36 and blood pressure 140/70 mm. Hg. The tongue was coated and the pharynx reddened. The trachea was in the midline. The chest was emphysematous; there was decreased expansion of the left lung with dulness, bronchovesicular breath sounds and sticky inspiratory rales over the right middle and both lower lobes of the lungs. The heart showed sinus tachycardia which was confirmed by electrocardiography. The abdomen was doughy and peristaltic sounds were markedly diminished. The liver and spleen were not felt. There was no clubbing or edema of the extremities.

"The blood Hinton test was negative. The white blood cell count was 15,900 per cu. mm. with 96 per cent neutrophils and the hematocrit was 50 per cent on admission. The urine contained 2+ protein and 6 to 10 white blood cells and occasional granular casts per high power field. Blood urea nitrogen was 68 mg. per cent. The sputum was green and tenacious, not copious in amount, and yielded an almost pure culture Pneumococcus type III, with rare alpha and beta hemolytic streptococci. Blood culture was negative. X-ray of the chest showed mottled areas of consolidation in the lower half of each lung field.

"The patient was placed in an oxygen tent, given intravenous glucose solution and intramuscular penicillin 120,000 units immediately and 40,000 units every three hours thereafter. This was supplemented for seven days with sulfadiazine 0.5 Gm. every four hours and sulfamerazine 0.5 Gm. every eight hours by mouth. He was maintained on digitalis 0.1 Gm. daily. The patient's temperature was normal by the third hospital day (figure 1), but on the seventh day spikes to 100.5° F. began to appear. On the tenth day the patient had a severe shaking chill and the temperature was found to be 104.5° F. and the white blood cell count 20,300 per cu. mm. Bronchial breath sounds were heard throughout most of both lung fields. Since this episode was thought to be due to a new invading organism, streptomycin 0.2 Gm. every three hours was added to the penicillin injections. Cultures of the nose, throat and blood all yielded growth of *Bact. aerogenes*, the former two sources also containing small numbers of *Staphylococcus albus*. The patient's temperature dropped promptly and then slowly reached

a normal level by the sixteenth day. The patient's subsequent course was long but uncomplicated. During this time his appetite and sense of well being improved, signs and x-ray evidence of pulmonary consolidation regressed and on the twenty-sixth day cultures of the throat grew only alpha streptococci. Follow-up films three months later still showed marked fibrosis at the site of his previous pneumonia."

"Case 4.—R. W., a 22 year old colored man was admitted to the hospital for the ninth time on March 5, 1948. The patient had been followed since childhood at the Children's Hospital and more recently at the Peter Bent Brigham Hospital for sickle cell anemia. There had been multiple admissions for hemolytic crises. In 1941 the patient was hospitalized for a pneumococcus, type III pneumonia of the left lower lobe which was successfully treated with sulfathiazole. For four days before the present admission the patient had a sore throat with mild cough and on the day of entry he developed fever, some shortness of breath and pain in the left anterior chest.

"Examination revealed a thin, acutely ill colored boy in moderate respiratory distress. The temperature was 102.4° F., pulse 104, and blood pressure 118/64 mm. Hg. There were many bronchial rales and slightly diminished breath sounds at the left base and axilla. The heart was enlarged with a rapid regular rate and a grade II systolic apical murmur. The spleen was not palpable and the remainder of the examination was not remarkable.

"The blood Hinton test was negative. The urine showed 1+ protein and occasional white blood cells. Hemoglobin was 10 Gm. per cent, hematocrit 30 per cent and the white blood cell count 26,000 with 88 per cent neutrophils and many sickle forms on smear. Except for a bilirubin of 5.0 mg. per cent blood chemical values were normal. Stool guaiac was negative. On admission a sputum culture yielded a heavy growth of *Diplococcus pneumoniae* with a few *Hemophilus influenzae* and *Neisseria catarrhalis*. X-ray of the chest revealed a triangular area of consolidation at the left base.

"Within 12 hours after treatment with penicillin, 50,000 units intramuscularly every three hours, the temperature was normal. Within 24 hours, however, the patient had a chill and the temperature rose to 103.6° F. The white blood cell count was 28,000 per cu. mm. and physical and x-ray examination revealed a spread of the area of consolidation in the left lower lobe. An immediate gram-stained smear of the throat and sputum showed predominance of gram-negative rods. On culture these were identified as *H. influenzae*. A few colonies of beta hemolytic streptococci were also cultured. Streptomycin, 175 mg. every three hours, or 1.4 Gm. per day, was given in addition to penicillin therapy, and during the next five days the temperature gradually dropped to normal. Sputum culture on the eighth day grew no *H. influenzae*. After 15 days of such combined chemotherapy the lungs cleared considerably and at the time of discharge on the twenty-second hospital day the patient was well."

The Results of Vaccination Against Tetanus in the Allied Armies During World War II — RAMON, GASTON— *Schweizerische medizinische Wochenschrift*, 79: 918 (September 24) 1949.

Antitetanic vaccination in order to confer sufficient antitoxic immunity should consist of three injections of tetanus antitoxin of convenient strength at intervals of at least two weeks, completed after a year or at the occasion of an injury by a booster injection. The vaccination against tetanus has been combined with that against diphtheria and also with that against typhoid and paratyphoid fever. Vaccination against tetanus has been made mandatory in the French Army. The efficacy of this method had been demonstrated experimentally and has been confirmed clinically during World War II. During the campaign of 1939 to 1940 no cases of tetanus occurred in vaccinated French soldiers, but the number of wounded was relatively small at that time and no definite evaluation of the efficacy of the method was afforded against the natural infection.

The results of the vaccination in the British Armies of the West were reported; only 6 cases of tetanus occurred among 103,000 casualties, while 25 cases occurred in the same area among a relatively small number of wounded German prisoners who

had not been vaccinated. With tetanus antitoxin treatment exclusively the morbidity from tetanus during World War I in the same area had been reduced to 1.5 per 1,000 casualties, thus it remained 25 times higher than during World War II.

The results obtained in the American Army are even more demonstrative and perfect. Vaccination was mandatory in the American Army and was carried out according to the author's technic. During the battle of Normandy in 1944 no cases of tetanus occurred although the soil of this area is known to be highly contaminated with tetanus bacilli; tetanus was relatively frequent among nonvaccinated wounded German war prisoners. In one hospital 20 cases among such prisoners were observed, with a mortality of 60 per cent in spite of treatment. A total of 12 cases of tetanus occurred in the entire American forces, 6 in the vast majority of vaccinated personnel and 6 in the minute minority of nonvaccinated personnel. In the Canadian forces a million men were vaccinated against tetanus and typhoid and paratyphoid fever; only 2 cases of mild tetanus and 1 fatal case occurred.

In view of these excellent results active immunization against tetanus should be propagated for all those who are exposed to this infection.

Oral Administration of Aureomycin in the Treatment of Urinary Infections — Rutenburg, Alexander M. and Schweinburg, Fritz B. — *New England Journal of Medicine*, 241: 698 (November 3) 1949.

Twenty-six patients were treated by aureomycin given orally.

"These cases comprised an unselected group of 26 acute and chronic urinary infections and included 5 with chronic renal insufficiency. Seventeen patients had had prior treatment with other antibiotics without clinical or bacteriologic improvement. Twenty had one or more of the following complications: hydronephrosis, calculi, ureteral stricture and prostatic obstruction. Obstructive disease, if present, was treated during aureomycin therapy.

"Twenty-one of the infections were due to a single organism, and 5 to more than one. The organisms involved were *Escherichia coli* (8 cases), *Aerobacter aerogenes* (12 cases), *Pseudomonas aeruginosa* (11 cases), *Proteus vulgaris* (1 case), hemolytic *Staphylococcus aureus* (1 case) and *Streptococcus faecalis* (1 case).

"Two grams of aureomycin were given daily in divided doses for four to six days, or longer, so long as bacteria were present. If cure did not result in two weeks, the drug was discontinued.

"Oral administration of aureomycin was generally well tolerated. In 3 patients with nausea and another with diarrhea, the reactions were mild, and the therapy was not interrupted. In 2 other patients vomiting prevented oral therapy, and the drug was given parenterally. The reactions varied with different lots of the drug. With the more recent lots, no gastrointestinal symptoms occurred. Renal injury was not observed during treatment. The nonprotein nitrogen was not increased in patients with renal insufficiency. Shortly after the drug had been started the urinary *p*H dropped to 4.5 to 6.0 and remained within this range as long as the drug was administered. Catheter specimens were cultured every second day, and treatment was continued for two or three days after the first sterile specimen. The patients were followed for 10 to 30 days and were considered cured only when two to five specimens of urine were found to be sterile after cessation of treatment. Anemia, leukopenia or thrombopenia did not develop. The white cell counts, which had been elevated before treatment, dropped to normal values within one or two days when treatment was successful."

"The clinical symptoms disappeared in all patients in a surprisingly short period —usually within 24 to 48 hours. It is noteworthy that the clinical improvement occurred whether the urine had or had not become sterile. In cases in which bacteria persisted, the clinical symptoms usually recurred when the drug was discontinued. The urine became sterile in 16 cases and remained so after the drug was discontinued.

"A close correlation was observed between the clinical result and the in vitro sensitivity of the organism to aureomycin. Thus, a rapid cure of the infection was obtained in every case in which the strain was sensitive, whereas partial or total

therapeutic failure resulted when the strain was resistant.

"The sensitivity of bacteria to a given antibiotic varies considerably, not only from species to species but also from strain to strain within a species. One hundred and thirty strains of various species, including many of those encountered in the present group of cases, were tested for sensitivity in vitro to aureomycin by the serial tube-dilution method. This method tests the response of a 24 hour broth culture inoculated with some 20,000 organisms of a particular strain to graded dilutions of the antibiotic. The lowest concentration of an antibiotic, in micrograms per cubic centimeter, that produces no macroscopically visible growth after incubation for 24 hours at 37° C. is considered the bactericidal titer. This titer for aureomycin was found to be as follows: The titer for 35 strains of *Ps. aeruginosa* varied from more than 200 to 0.0125 micrograms per cubic centimeter, over half the strains requiring more than 50 micrograms per cubic centimeter. The titer for 30 strains of *P. vulgaris* ranged from over 200 to 0.0125, a third of the strains requiring more than 50 micrograms per cubic centimeter. The titer of 25 strains of *Esch. coli* and of 20 strains of *A. aerogenes* ranged from 6.25 to 0.0125 micrograms per cubic centimeter, but with an occasional strain requiring more than 200. The titer of 10 strains of hemolytic *Staph. aureus* and of 10 strains of beta hemolytic streptococcus were inhibited by 0.4 to 0.0125 microgram per cubic centimeter. If the growth of a strain was completely inhibited by a concentration of less than 50 micrograms of aureomycin per cubic centimeter of culture, the strain was considered sensitive. If the growth was completely inhibited by a concentration of 50 micrograms or higher per cubic centimeter of culture, the strain was considered resistant.

"There was recurrence of infection in 2 patients. The first had chronic urinary retention and acute pyelonephritis due to *A. aerogenes* that was very sensitive to aureomycin in vitro. He responded rapidly to aureomycin therapy, but twice at intervals of three weeks the infection recurred. Both relapses yielded promptly to the drug.

"The second patient, with severe cardiovascular disease, renal tumor and a hypertrophied obstructing prostate, had an infection due to *Ps. aeruginosa* that was very sensitive to aureomycin in vitro. Twenty days after the drug had been discontinued the infection recurred and again responded rapidly to the drug.

"In a third patient with chronic cystitis and pyelonephritis due to *Esch. coli*, as well as renal insufficiency and a blood nonprotein nitrogen varying from 80 to 120 mg. per 100 cc., the infection was cured within 48 hours. The urine remained sterile for 28 days. Reinfection occurred with *A. aerogenes*. A second course of therapy promptly sterilized the urine which remained sterile for the next 14 weeks, when observation was discontinued.

"In these 3 patients, bacterial resistance to aureomycin did not develop.

"A fourth patient, with a vesicovaginal fistula and a mixed urinary infection due to *A. aerogenes*, *Str. faecalis* and *Ps. aeruginosa*, improved clinically, but only the first two of these organisms were cleared from the urine. *Ps. aeruginosa* remained. In a fifth patient with mixed infection one organism (*A. aerogenes*) was cleared but the other (*Ps. aeruginosa*) was not. This patient also showed clinical improvement.

"There were 5 bacteriologic failures in monovalent infections, 1 due to *Esch. coli* and 4 to *Ps. aeruginosa*. In these cases the bacteria were resistant to aureomycin in vitro.

"Of 34 strains of bacteria found in the urines of the 26 patients, all 12 strains of *A. aerogenes*, 7 or 8 strains of *Esch. coli* and 1 strain each of *P. vulgaris*, hemolytic *Staph. aureus* and *Str. faecalis*, were eliminated from the urine. Of 11 strains of *Ps. aeruginosa*, 5 that were sensitive to the drug in vitro were eliminated, whereas 6 that were resistant in vitro were not."

Pediatrics

Prophylaxis of Whooping Cough — Fox, Max J. and Snartemo, Reuben —*American Journal of Diseases of Children,* 78: 677 (November) 1949.

"From January 1, 1933 to December 31, 1948 there were 37,774 cases of whooping cough among the residents of the city of Milwaukee. The incidence of the disease followed a rough cyclic pattern, with peaks occurring every four to five years. Increased mortality rates did not occur in the years of higher incidence. Indeed, the determinant which was of greatest significance was the patient's age. The extreme disproportion in the mortality rates between early infancy and later childhood is most strikingly illustrated by the fact that while children in the first year of life account for only 7.85 per cent of the total number of cases reported (2,966 of 37,774), they provided 72.4 per cent of the deaths (71 of 98)."

Of 36 deaths, 13 occurred in infants under 3 months of age, 15 in infants under 4 months of age and 19 in infants under 6 months of age. "In 1941, the Milwaukee Health Department began to record deaths from whooping cough by age in months. An analysis of 34 deaths occurring in the entire city of Milwaukee for the years 1941 to 1948, inclusive . . . . reveals that 8 deaths occurred in infants under 3 months, 13 in infants under 4 months, 17 in infants under 6 months and 27 in those under 12 months of age."

"The mortality rate in children hospitalized at South View Hospital is seen to be over seven and a half times as great in those under 1 year of age as in those over 1 year old, with 52.8 per cent of the deaths occurring in infants under 6 months of age. Furthermore, citywide mortality statistics do not vary greatly from those of the hospital. During the past five years in Milwaukee, only 2 deaths from whooping cough have occurred in infants between the ages of 1 and 2 years, and there have been no deaths in children over the age of 2 years. It is also significant that Litvak and his co-workers, in reviewing 40 cases of cerebral complications in whooping cough, observed that 50 per cent of the patients in whom these complications developed were under 1 year of age."

The age group most vulnerable to this disease is not protected by present prophylactic measures, and the question arises of how present immunization schedules may be altered in order to bring about a decrease in mortality due to whooping cough. "It is extremely important to know in what manner adequate protection can be extended to children in this age group of early infancy, especially to those in the first six months of life. . . . This group can hardly be protected by immunizations which do not begin until the sixth month, and the problem crystallizes into the question of how early the immunization procedure can begin to call out an active immunity and offer some valuable degree of clinical protection."

While the antigen-tissue clash may be severe and, at times, overwhelming, most infants manifest sufficient function of the reticuloendothelial system to survive. "This would then indicate that successful immunizations could be done at an early age."

The writers agree that an immunization response is more readily obtained after 6 months of age than during the first few weeks of life, but at the same time they point out that the percentage response and the degree of response, even in the very young infant, are at times lifesaving. They know that those children under 6 months of age who contract whooping cough after being immunized tend to have only a mild form of the disease. "Whether initial efforts at immunization begin at 3 months of age, at 1 week or in the pregnant mother should depend, not on a worldwide, nationwide or statewide policy, but on local immunization schedules especially fitted to suit individual circumstances. In children whose home environment is such that they can be sheltered from the common infections, the physician may well wait with their immunization program until the sixth month, when a high degree of success may be expected.

When a probable exposure can be anticipated, however, as it can in crowded districts and where high rates of incidence of whooping cough prevail, then to wait until the sixth month to give infants protection is often to have waited too long. In such situations early immunization is imperative." Subsequent booster doses would then serve to prolong and reenforce the immunity obtained. Furthermore, such early immunization programs are made considerably more attractive by the fact that there is a reliable agglutinogen skin test (Flosdorf) which not only is helpful in differentiating the immune from the nonimmune but also tends to produce a prompt recall of any potential antibacterial immunity.

Lipoid Nephrosis Complicated by Homologous Serum Jaundice — ROSENBLUM, ARTHUR H., LANDER, HERMAN AND POPPER, HANS — *Journal of Pediatrics,* 35: 465 (October) 1949.

"The clinical and pathologic findings on a 3 year old girl, who developed fatal fulminant infectious hepatitis from the administration of plasma as treatment for a clinically 'pure' lipoid nephrosis, are described."

"A. B., a 3 year old white female child, entered . . . . hospital on November 12, 1946, with a history of insidious onset of edema and ascites approximately one month in duration. She had been perfectly well except for measles and chickenpox during the first year of life and pertussis during the second year. There was no history of an antecedent illness, either of a chronic or acute nature, which may have precipitated the disease.

"On physical examination the child showed the characteristic appearance of a nephrotic with a moderate amount of generalized pitting edema, ascites, and pallor. There were no other significant physical findings except for a palpable, nontender liver. The urine showed 4 plus albumin, specific gravity 1.034, acid reaction, no sugar or acetone, no blood to chemical or microscopic test, and a few pus cells in the centrifuged sediment. The complete blood count was within normal limits, with a hemoglobin concentration of 13.5 Gm. (Sahli), and a red count of 4.41 million. The total serum protein concentration was reduced to 4 Gm. per 100 cc. with reversal of albumin-globulin ratio; the nonprotein nitrogen was 37 mg. per 100 cc. The sedimentation rate was 30 mm. per hour (Wintrobe). The Kahn test was negative.

"The clinical course showed a progressive increase in edema and ascites until the seventy-third hospital day, when weight loss began. At various times during the first half of her hospital stay (from the tenth to the fifty-third day), the child received infusions of concentrated pooled human plasma with no appreciable change in her edema. She was given one half of a Mercupurin suppository on the thirty-first, thirty-seventh, and fiftieth hospital days with little effect. On the fifty-third hospital day, ½ cc. Mercupurin injected intravenously caused a transient weight loss of 1.5 pounds. From the seventy-eighth to the eighty-fourth hospital day salt-poor human albumin was injected daily in amounts of 25 to 35 cc. The subsequent weight loss was rapid and pronounced. However, there was a mild diuresis prior to the institution of this therapy, and it cannot be stated with certainty that the response was produced by the therapy. On the eighty-fifth day, at which time the child appeared edema free, the total proteins had risen to 5.1 Gm. per 100 cc.

"The liver remained enlarged during the entire hospital stay, but not tender. Just prior to her hospital discharge, the cephalin flocculation was 0 and the thymol turbidity 5.3. The blood pressure was occasionally moderately elevated, 130/85 on the sixty-eighth hospital day, and 112/78 on the eighty-fourth hospital day. However, the significance of such occasional deviations from the normal is questionable particularly as the child was fearful of blood pressure determinations. Urea clearance tests showed 95 per cent of normal on the twenty-ninth hospital day, and 100 per cent on the thirty-third hospital day.

"On the ninety-seventh hospital day the twenty-fourth hour urine specimen showed only 270 mg. albumin. At no time during her hospital stay or in subsequent clinic visits did her urine show blood, using the benzidine and orthotolidine tests. On 1 specimen, an occasional red cell was noted in the centrifuged urine. The non-

protein nitrogen remained consistently within normal limits except for a finding of 46 mg. per 100 cc. on the seventieth hospital day, at which time the anasarca was close to its maximum.

"Subsequent to release from the hospital on the ninety-eighth day after admission, this child was seen in the Clinic on February 28, 1947, and March 28, 1947, in excellent condition. Her weight remained stationary, slightly above that on discharge from the hospital. It was felt that the slight increase could be ascribed to improved nutrition. Her blood pressure was 110/60 on February 28, and 105/60 on March 28. Urine showed one plus albumin and occasional white but no red cells.

"On April 6, 146 days after her first admission, the child was again brought to the hospital. This time she was comatose, and markedly jaundiced, but showed no edema. She vomited considerably. She had been febrile for one week, and had been taking a sulfa medication for five days. Four days prior to admission her urine became brown and her skin yellow. A few hours after admission to the hospital the patient died.

"Autopsy.—The peritoneal cavity contained approximately 50 cc. of a sanguineous, yellow fluid. The lungs were dark purple-red, congested, and edematous. The pleura revealed multiple ecchymoses. Trachea and bronchi contained some sanguineous, mucopurulent material. The heart was of normal size, the myocardium pale, the mitral valve edematous. The purple-blue spleen weighed 75 Gm. and was of reduced consistency. The architecture on the cut surface was somewhat obscured.

"Histologically, the large follicles had small germinative centers; the pulp revealed marked reticulum and endothelial cell hyperplasia. The pale pink liver weighed 550 Gm.; its inferior edge was sharp. The consistency was unusually low and the organ flattened out if placed on a table. The architecture was mostly obscured; only in circumscribed areas was it well preserved or even exaggerated due to a distinct red color of the lobular centers. The histologic structure of the liver cell cords was entirely missing. However, the arrangement of the central and peripheral fields was well preserved although the fields were closer to each other than usual. The liver cells within the lobules were almost entirely missing. Only toward the periphery were a few isolated polygonal liver cells seen, which revealed diffuse coagulation necrosis of the cytoplasm and occasionally small fat droplets. On the lobular periphery liver cells were arranged in irregular cords which often revealed a wide bile capillary in their center. These cords simulated proliferated bile ducts. The meshes of the intralobular connective tissue framework were crowded with mesenchymal cells, the larger of which revealed a superficial similarity to liver cells. They contained granular bile pigment and phagocytosed cell fragments. In addition, smaller mononuclear cells were seen, such as lymphocytes and histiocytes. The segmented leukocytes were mostly eosinophilic. In the portal triads and to a lesser degree around the central vein, there was a dense infiltration of similar, round, cellular elements, many of them pigment carrying. The slightly dilated sinusoids contained a moderate number of red cells. A few were also seen in the tissue spaces. The reticular fiber framework was intact; in a few places it was collapsed but nowhere scarred. The widened gallbladder bed was edematous. The portal lymph nodes were markedly enlarged and revealed extensive reactive hyperplasia. Pancreas and lipoid-rich adrenals revealed no abnormalities. The pale pink-gray kidneys were large, weighing together 150 Gm. Their surface was smooth. On the cut surface the markings were well recognized. Histologically the architecture was intact. The glomeruli revealed, in general, normal cell content. Only occasionally some glomerular loops appeared matted together and were surrounded by a continuous layer of small cells with dark nuclei in palisade arrangement. The pericytes appeared in places proliferated; nowhere however, did the endothelial cells show proliferation. The basement membrane was mostly normal although in some loops it appeared thickened and the hematoxylin-eosin sections appeared diffusely red. In MacGregory or glycoprotein stains, such loops revealed a double contour of the basement membrane. The tubular epithelium was normal except for regularly arranged, fine vacuoles (apparently after dissolution of fat) on

the base of the epithelium of the proximal convoluted tubules. There was no albuminous material in Bowman's space but some in the tubular lumen in form of densely staining granules. Vessels and interstitial tissues were normal. Urogenital and gastro-intestinal tracts revealed no changes. Examination of the head was not permitted."

Asphyxia and Shock in the Newborn—GOVAN, A. D. TELFORD — *Lancet*, 2: 839 (November 5) 1949.

"An attempt has been made to define the changes in stillbirth associated with shock and asphyxia. Over nine months about 400 necropsies were performed at the Glasgow Royal Maternity and Women's Hospital on cases of stillbirth and neonatal death. From these, 116 stillbirths have been selected. According to the post-mortem picture these appeared to form three distinct groups.

"Group 1.—In the first group, accounting for 30 of the 116 cases, the child most commonly presented at birth the appearances of asphyxia pallida. Often, however, there were irregular patches of slight cyanosis on the face and limbs.

"The pectoral muscles were usually pale, but occasionally they contained patches of haemorrhage. In a few cases haemorrhage was also found in the anterior mediastinal tissues and on the parietal pericardium.

"The myocardium was commonly pale, but sometimes showed an irregular patchy congestion. In many of these cases, however, the most striking feature was haemorrhage, forming a broad band along the atrioventricular sulcus on the posterior aspect of the heart, and commonly extending on the right side to the anterior surface and downwards along the coronary vessels to the apex. The coronary arteries were generally empty, but the accompanying veins were commonly distended with blood. In some cases haemorrhage was more diffuse, arising in patches over the surface of the right ventricle. Haemorrhages were also seen on the adventitial coat of the ascending aorta. Very little blood was found in the cavities of the heart. In a few cases tiny subendocardial haemorrhages were found on the medial wall of the left ventricle a little below the aortic valve.

"The thymus showed typical changes. It was always pale but often spotted with small round distinct haemorrhages. The lungs were almost invariably cyanosed and had sometimes collapsed against the vertebral column. The pleural cavities frequently contained a little excess of fluid, and on the visceral surface there were numerous haemorrhages in the form of either fairly large flame-shaped patches or a diffuse close-set rash of tiny petechiae giving a rather 'tabby-cat' appearance to the organ. Small haemorrhages in the substance of the lungs were also common. Haemorrhage was sometimes present beneath the parietal pleura on the diaphragmatic surface, and similar effusions of blood were found on the under surface of the diaphragm and along the ligamentum teres.

"The liver parenchyma was usually rather pale, but in some cases there was subcapsular congestion with superficial haemorrhages mainly on the upper surface.

"The spleen was small, but showed little change on naked eye examination, though in a very few cases intracapsular haemorrhages similar to those on the liver were present.

"The adrenal glands presented a variety of appearances. Most commonly the cortex was very pale brown and seemed to contain none of the usual yellow and rather refractile lipoid, while the medulla was grey. In a few cases capillary haemorrhages were seen in the cortical tissue, while in others yellow lipoid was present as a thin subcapsular band and there was congestion of the deeper cortical zones.

"A rather similar variation of the vascular pattern was found in the kidneys. Commonly there was generalised pallor of both cortex and medulla, but in many the medulla was relatively congested and the juxtamedullary zone of the cortex definitely so. In others tiny haemorrhages were present just beneath the capsule.

"Usually little change could be seen in the intestines or peritoneal cavity; in some cases there was a small excess of fluid, and in a very few there were petechial haemorrhages on the serous surface of the bowel. The colon was distended with meconium.

"The brain was usually pale and oedematous. Tentorial tears with varying

amounts of subdural haemorrhage were found in a third of the cases, but the haemorrhage was severe in only a single case. Slight subarachnoid oozing over the cortex was found in 6 per cent of cases. In most, however, no gross cerebral injury could be found.

"Antepartum haemorrhage, which occurred in 14 of the 30 cases in this group, appeared to be the most common associated factor. In 13 the haemorrhage was accidental; in only 1 was it due to placenta praevia. In 9 cases there had been malpresentation, corrected by internal version, with delivery manually or by forceps. In another 7 the child was delivered by forceps, but in each instance the pregnancy was complicated by toxaemia. There were 8 premature births in this group; the postmortem appearances did not vary from those already described.

"Group 2.—A very different appearance was presented by stillborn children of the second group. Here there was pronounced general cyanosis, with oedema of the face in some cases.

"The pectoral muscles were congested, but there was no sign of haemorrhage either in these or in the mediastinum. Congestion of the myocardium was extensive, but there was no epicardial haemorrhage. The right side of the heart was usually engorged with blood, but otherwise the heart appeared normal.

"In the thymus no gross abnormality, apart from congestion, was found.

"The lungs were bulky and cyanosed. The lung substance was firm; the edges of the lobes were usually sharp, and foetal lobulation was absent. Occasionally a few superficial petechiae were found on the pleural surfaces.

"There was severe congestion of the abdominal organs, including the liver, spleen, and kidneys. Haemorrhage was infrequent, and the congestion was generalised—not confined to one part of the organ as in the first group. Thus in the kidneys both the cortex and medulla were congested, and indeed the cortex was the more congested of the two zones.

"The adrenals showed intense congestion of the medulla and inner cortex with occasional small haemorrhages; lipoid was reduced to a very thin and patchy layer just under the capsule.

"There was well marked congestion of the brain and meninges. In about 40 per cent of cases tentorial tears were present, but haemorrhage was not found in any significant amount. The vein of Galen was distended in every case but 1, where the subdural haemorrhage was a little more extensive.

"Of the 24 cases in this group, death in 13 appeared to be due to an abnormality of the cord—such as cord wound tightly several times round the neck, prolapsed and compressed cord, and short cord with traction on it throughout labour. In 5 death was due to occlusion of the trachea by aspirated vernix or meconium or by a plug of mucus. In 6 there had been delayed labour which was allowed to proceed without interference; 2 of these were associated with malpresentation, while each of the remaining 4 was the second of twins. Maternal toxaemia was present in 5 cases, but did not appear to bear any direct relation to the cause of death. All of these babies were mature.

"Group 3.—Most of the cases (62) fell into the third group, which seemed to have features in common with both the other 2. The child was always cyanosed at birth and occasionally had a petechial rash on the skin—most often on the neck and chest.

"Haemorrhage into the anterior mediastinal tissues was common. The myocardium was patchily congested with pronounced distention of the veins. A band of haemorrhage similar to that seen in group 1 was present along the posterior atrioventricular sulcus, extending anteriorly to the interventricular line, and then passing down to the apex of the heart. Haemorrhages were also present on the ascending aorta up to the reflection of the pericardium. The right side of the heart was usually distended with blood. In a few cases subendocardial haemorrhages were found in the left ventricle.

"Punctate haemorrhages were present on the thymus, which was grossly congested.

"As in the other groups, the lungs were cyanosed. Pleural haemorrhages, similar to those in the first group, were numerous. The lungs were bulky and firm and intrapulmonary haemorrhages resembling infarcts were common. The air passages sometimes

contained a blood-stained discharge, which was very occasionally seen at the nostrils. The pleural cavities contained a little excess of serous fluid, and there were haemorrhages on the diaphragmatic surface.

"The liver was very congested, and haemorrhages occurred in two forms: (1) commonly as large blood bullae raising the capsule from the underlying parenchyma, which in 2 cases had ruptured with a subsequent haemoperitoneum; and (2) occasionally as a diffuse rash of petechial haemorrhages beneath the capsule. Sometimes both types of haemorrhage were seen.

"Subcapsular petechiae were also found in the spleen, and haemorrhages in the splenic pulp gave the organ a slightly nodular appearance.

"In the adrenal glands medullary and subcortical congestion associated with capillary haemorrhage was pronounced, and in 2 cases an apoplectic appearance was evident. Lipoid appeared to be scanty or absent.

"The kidneys were usually congested, but the congestion was occasionally confined to the medulla and juxtamedullary regions; cortical haemorrhages were common.

"The intestines were congested and in a few cases petechiae were found on the serous surface of the small intestine. An excess of straw-coloured fluid was present in the peritoneal cavity.

"In 27 of the 62 cases there was no structural change in the brain or meninges. In all the cases the brain was very wet and there was an excess of cerebrospinal fluid; many showed congestion of the intracerebral vessels. Tentorial tears were present in 20 cases; but in 12 of these haemorrhage was absent, indicating that the tears had probably occurred post mortem. This suggests that in this group tentorial tear is not of primary importance. In 9 instances subarachnoid haemorrhage occurred. This was always over the vertex; sometimes it was diffuse, but commonly it took the form of small discrete flame-shaped effusions from the superficial vessels. Gross intraventricular haemorrhage was found in 2 cases, and in a third there were haemorrhagic blebs beneath the ependyma on the wall of the lateral ventricles. Of the remaining cases, 2 had been subjected to craniotomy and the third was anencephalic.

"In the mother the commonest complicating factor in this group was toxaemia, including eclampsia and accidental haemorrhage; this arose in 54 per cent of cases. Maternal shock was the next most common complication; in 20 cases this was due to accidental haemorrhage, in 5 to placenta praevia, and in 2 to ruptured uterus. Eclampsia occurred in 4 cases. Prolonged labour was often a prominent feature, but this was always associated with some other factor such as toxaemia, antepartum haemorrhage, difficult forceps delivery, or caesarean section. In this group there were 16 premature babies, of whom 6 weighed less than 4 pounds. Prematurity, however, did not seem to influence the postmortem appearances. In neonatal deaths cerebral haemorrhage appears to be particularly associated with prematurity, but in this group of stillbirths only 2 of the 9 cases with subarachnoid haemorrhage were born prematurely. Of the 3 infants with haemorrhage in or around the ventricles, 1 was mature."

Methods Used in Treatment of Diarrhea with Potassium and Sodium Salts — Flett, James, Jr., Pratt, Edward L. and Darrow, Daniel C.—*Pediatrics*, 4: 604 (November) 1949.

"The actual procedures used in the treatment of 153 cases of diarrhea with potassium chloride in addition to the other established therapeutic methods are described. . . . The total number, 153, was divided somewhat arbitrarily into 60 mildly ill, 28 moderately ill and 65 severely ill patients."

"About 88 per cent were less than 6 months of age and 71 per cent were under 2 months."

"The treatment is briefly described under five headings:

"1. Restoration of circulatory and renal function is attained chiefly by intravenous injection of a mixture of about equal parts physiologic saline and glucose in water (40 ml./Kg. body weight) followed by a transfusion of blood or plasma (30 ml./Kg.). Only the severe and some of the moderate cases require this therapy.

"2. Replacement of deficits of water d electrolyte is accomplished chiefly by e subcutaneous injection of a mixture ntaining Na 120 mK, K 35 mM, Cl 5 mM, and lactate 52 mM/1. This mix- re is called K-lactate. . . . The injection carried out by a drip regulated to a rate quiring four or more hours for the entire se for one day (80 ml./Kg. body weight r the initial day of treatment). The in- ction of K-lactate is given subcutaneous- because it is felt that this lessens the ngers of a sudden rise in serum potassi- n concentrations to toxic levels. In se- re cases, the administration of K-lactate delayed until the intravenous therapy s produced improvement in the circula- on but the injection is usually started thin an hour. If oliguria is not overcome thin an hour after starting the adminis- ation of K-lactate, the rate of injection ay be decreased. Experience has indicat- that the slow rate of injection makes e dangers of potassium intoxication neg- gible even in severely dehydrated pa- nts.

"Patients who are less severely ill re- ive hypodermoclyses of K-lactate to- ther with infusions of physiologic saline d glucose in water but no transfusions blood.

"Those patients who seem unlikely to mit and who will take fluids well by outh are given orally a mixture of 1 part -lactate added to 2 parts 5 per cent glu- se in water. One hundred and fifty l./Kg. body weight has been shown to sufficient to replace in one day the ficits of H_2O, Na and Cl if the patients e so treated. Potassium deficiency is not mpletely restored for as long as six days.

"3. Restoration of serum HCO_3 is satis- ctorily accomplished by the above meth- ls. Additional administration of $NaHCO_3$ lactate is seldom if ever required in the idosis of diarrhea.

"4. Maintenance of water for obligate penditure is accomplished by glucose lutions. In severe cases, the intravenous jection is continued with 5 or 10 per cent ucose in water so as to make the total take of glucose in water 100 or more l./Kg./day. If intravenous therapy is ntinued beyond the first day, about the me amount of 5 or 10 per cent glucose water is combined with a subcutaneous injection of K-lactate 50 ml./Kg. In mild and moderate cases, replacement of electrolyte and provision for water for obligatory expenditure is accomplished by oral administration of the mixture of 1 part K-lactate and 2 parts 5 per cent glucose in water, 150 ml./Kg. This oral mixture is used in practically all severe cases as well as mild cases after the first 24 hours.

"5. Milk feedings are omitted in all patients for 24 hours or until the stools are no longer watery and voluminous. Fever, nausea, dehydration, abdominal distention and lack of appetite are considered contraindications to milk feedings. The food mixture in practically all patients is made from whole milk and skimmed milk powders together with sufficient water to make a mixture containing fat 1.8 per cent and protein 3.5 per cent. Dextrimaltose is added to this to make a 10 per cent mixture. The basic mixture may be regarded as essentially the same as 10 per cent dextrimaltose added to boiled cow's milk containing fat 2 per cent. The amount of the basic milk mixture containing the desired number of calories is always diluted with sufficient H_2O to cover a high rate of water expenditure. The total volume is usually 150 ml./Kg./day. During the first day of milk feeding, the caloric intake is small (10 to 20 cal./Kg./day). The proportion of milk in the same total volume of fluid is increased by 10 to 20 cal./Kg./day according to the reaction of the patient. The intake of food is not increased beyond 90 to 100 cal./Kg./day until several days' trial indicates that a larger intake is indicated. The feeding intervals are three to four hours. If all the food is taken, as is the case if milk feedings are not started too soon, the water requirement is fulfiled. Only in rare instances does the institution of milk feeding lead to sufficiently watery stools so that dehydration develops. As much as 170 ml. of fluid/Kg./day may be required if losses of water are high in both stools and sweat. This will only occur in hot weather when stools remain watery.

"In order to promote the retention of K, the milk mixtures providing less than 70 cal./Kg./day are fortified with KCl 1.0 Gm. added to the total mixture for 24 hours.

"The authors have attempted to simplify the procedures as much as possible

Table I
Per Cent of Cases Receiving Parenteral Treatment

Days	Blood or Plasma			Intravenous Glucose			Subcutaneous 'K=lactate		
	1	2	3	1	2	3	1	2	3
Mild	5	7	4	22	4	4	32	11	4
Moderate	22	3	0	50	6	6	50	15	9
Severe	75	38	10	85	28	13	85	44	7

so that effective treatment can be carried out by physicians without laboratory help or unusual facilities for parenteral therapy. This has led to minor changes in the application of the procedures as experience has indicated that prolonged parenteral therapy is not necessary."

"Table I shows the proportion of each group receiving parenteral therapy during the first three days. About 75 per cent of the severe cases received blood or plasma transfusions as soon as feasible after admission. There has been no noticeable tendency to decrease this proportion in recent severe cases. Those severe cases not receiving transfusions may usually be regarded as ones in which the subsequent course indicated that the severity of the disease was underestimated on admission, or cases with prolonged diarrhea which were regarded as severe despite absence of the profound disturbances on admission. Some of the patients who were not transfused on the day of admission received blood on the second day. The recent cases have seldom received blood on the second day if transfusion was employed on the first day. The tendency to use transfusions on the first day has been definitely less in recent cases in the moderate group. The mild cases have received no transfusions of blood on the first day during the last year and a half. Plasma was given in some recent mild cases of diarrhea of the newborn infant because of the tendency for the diarrhea to persist for about seven days. In these cases plasma was given to support nutrition rather than the circulation.

"Infusions of glucose and saline were used in 85 per cent of the severe cases. There has been no tendency to decrease this proportion appreciably in the recent patients. However, infusions have been used less frequently on the second da during the last year and a half. Hypo dermoclyses of K-lactate have been em ployed in all patients receiving infusion but recently the clyses and infusions hav been less frequent on the second day i severe cases.

"About 50 per cent of the moderat cases received infusions and clyses on th first day. During the last year and a ha this proportion has greatly decreased. A mentioned above, hypodermoclyses and in fusions have been omitted in all mild case during the last year and a half."

As for fluid intakes the severe cases re ceived about 200 ml./Kg. body weigh during the first 24 hours while the moder ate and mild cases received about 15 ml./Kg. "On the second day the sever cases received somewhat more fluid tha the others but thereafter the difference i fluid intake was insignificant. On the firs day some of the severe cases receive 300 ml./Kg./day, 1,350 ml. and 1 as littl as 150 ml. Two hundred and fifty ml./Kg were frequently given. During the firs 24 hours, the moderate cases sometime received as much as 200 ml./Kg./day an sometimes as little as 150 ml./Kg./day."

Concerning types of fluid administere 10 per cent glucose in water was use intravenously in most cases, a 5 per cen solution was used in a few. "The ora mixture of 1 part K-lactate and 2 part glucose employed a 5 per cent glucos solution in most cases but a 10 per cen solution was used in a few."

"In order to replace the initial defic of extracellular electrolyte, somewhat mor K-lactate was given during the first tha the second day. The amount of glucos in water is kept about the same durin the first two days since the water require

nt for insensible losses and for urine mation remains about the same."

Twenty-five per cent of the severe cases re given the mixture of 1 part K-lactate d 2 parts 5 per cent glucose on the first y and 86 per cent on the second day. he mild and moderate cases received l fluids earlier—about 97 per cent by e second day. . . . Oral fluids have been rted sooner in the cases treated recently."

"None of the patients received milk for hours but milk was started in half the ld cases on the second day, about 25 r cent of the moderate cases and 5 per nt of the severe ones. Milk has been rted by the fourth day in practically all ses." Full caloric feedings were attained 4 to 12 days in the mild and moderate ses and 6 to 12 days in the severe ones. here has been no appreciable tendency start milk earlier in the recent cases.

"The admission weights of the babies in is series were compared to the normal pected weights for babies of similar age. making this evaluation, the babies too ung for their weights to reveal under- trition prior to the onset of their acute ness were eliminated. The severely sick bies were 30 per cent under the expected ight while the mild and moderate cases re 17 per cent under the expected ight. The babies of this series who succumbed to their illness weighed on admission 47 per cent less than their expected ights. . . . Diarrhea is a much more rious hazard to undernourished infants.

"It is difficult to determine the character the stools by reviewing the records. general, the diarrhea had abated during e 24 hours prior to beginning milk feeding.

"There were 13 children who suffered lapses or developed diarrhea for a second time. Seven of these were in the severe group and 3 in each of the other oups. Most of the babies who relapsed d been considered malnourished before e onset of the initial diarrhea. At least were known to be 'feeding problems'; babies appeared to relapse when increase in the milk mixture was instituted er a short period of time. Two others owed an exacerbation of the diarrhea nen the caloric intake was abruptly anged from 80 to 110 cal./Kg. body ight/day. Three relapses may have been associated with inadequate intake of fluid in the first day or two of treatment.

"The mortality was 6 per cent and study of the fatal cases indicated that a large proportion of these cases apparently died from nutritional injury developing before the onset of the diarrhea or from injury as a result of dehydration developing before treatment was started.

"The serum bicarbonate returns to normal somewhat more slowly than when larger doses of sodium bicarbonate (or lactate) are given. However, the absence of alkalosis, the infrequency of low serum calcium and the infrequency of the 'post-acidotic state' suggest that slow restoration of the concentration of serum bicarbonate may be advantageous.

"In no instance was low concentration of potassium in serum encountered. On the other hand, serum potassium remained normal or slightly high during recovery. In no instance were symptoms referable to potassium intoxication encountered and in no instance was death associated with high concentration of potassium in serum."

"During the past six months the authors have used for oral administration a granular salt mixture. When added to the recommended amount of water, a liter contains glucose 50 Gm., Cl 24 mM, citrate 7 mM, phosphate 5 mM, Na 24 mM, K 28 mM, Mg 2 mM and Ca 2 mM. The solution is slightly acid and has a pleasant taste. It has been substituted for the oral mixture of 1 part K-lactate and 2 parts 5 per cent glucose. While the need of the ions not present in the latter solution has not been demonstrated, the low concentration of phosphorus in serum which frequently develops following treatment for dehydration suggests that phosphate may be indicated. Deficits of Ca and phosphate in bone may occur. . . . The authors' evidence that there is no true deficit of cellular phosphate is based entirely on balances of patients who recovered and does not fit in with the evidence that some fatal cases show low concentration of phosphate in muscle at autopsy. Magnesium is lost in fairly large amounts in the stools. Thus, it is likely that the granular salt mixture provides some advantages.

"All that can be stated at present is that the infants take the solution made from the granular salt mixture readily

and look as well as with the other mixture. There have been no deaths since the mixture was started, but the death rate was already so low that this method of evaluation is meaningless in establishing an improvement in results."

The Relations Between Acetonemic Vomiting and Migraine—VAHLQUIST, Bo—*Annales paediatrici*, 173: 272 (October) 1949.

There are certain points of contact between acetonemic vomiting and migraine in children; both involve syndromes which appear in the form of attacks frequently in individuals with signs of nervous lability, and the vomiting which dominates the syndrome of acetonemia may be intense in migraine as well, particularly in preschool children. Several authors were of the opinion that a close relationship exists between the two affections, and the frequency of migraine in the families of children with acetonemic vomiting has been stressed as well as the fact that in some children the attacks of acetonemic vomiting are gradually replaced by typical attacks of migraine. Mere coincidence may be dealt with, however, and detailed studies on a material of 4,500 individuals of different age groups are being undertaken for clarification of this problem.

The author collected the material of cases of acetonemic vomiting from two pediatric clinics and studied the incidence of migraine; only cases with recurrent attacks of vomiting of at least one days' duration without apparent cause like infectious diseases were included, amounting to only 61 of the 299 cases in which a clinical diagnosis of acetonemic vomiting had been made. Control examinations were made in 24 of these cases.

The first of several characteristic cases reported concerned a man, who had been treated for acetonemic vomiting at the age of 9, and who was studied at the age of 34. His mother and one of his sisters suffered from asthma and a sister of his father from cholelithiasis. There was no family history of migraine. The patient had experienced several attacks of severe vomiting of four to seven days' duration yearly between the ages of 7 and 14, and later suffered from nephritis and articular rheumatism. He never experienced migrai and showed no definite signs of nervo lability.

The second case concerned a girl w had been treated for acetonemic vomiti at the age of 10 and was examined at t age of 16; her father had suffered fre gastric pain on excitement, and a sist suffered from urticaria, but there was family history of migraine. The patie had suffered from attacks of acetonem vomiting between the ages of 6 and 1 with or without preceding infection; t attacks came at times at intervals of on one to two months, and lasted one da to one week. The patient never suffere from migraine. The patient considered he self nervous and her clinical history me tioned a typical neuropathic aspect but definite signs of nervous lability we demonstrable. The patient was slightly h poplastic for her age and had a low bloo pressure (95/60 mm).

The third case concerned a man, age 18 at the time of examination, who ha been treated for acetonemic vomiting the age of 6. His mother and matern grandmother suffered from attacks to h interpreted in all likelihood as migrainou in nature. The patient suffered from dia rhea and abdominal pain on excitemen but not from migraine. The acetonemi attacks had been severe and had occurre between the ages of 4 to 12, from s to eight a year. Examination showed mo erate vasolability but no other signs nervous lability, normal reflexes and blood pressure of 110/60 mm.

The fourth case concerned a boy treate for acetonemic vomiting at the age of 1 who was examined at the age of 13. Th mother and maternal grandmother suffere from typical migraine and the father fro a peptic ulcer. The patient himself ha suffered from parotitis with meninge irritation, was active and sensitive, an experienced diarrhea on excitement. Be tween the ages of 5 and 9 he had ex perienced a total of 10 attacks of violen vomiting and abdominal pain, with suc den onset and lasting several hours t one day. During the past few years h developed attacks of a different kind, wit occasional photophobia and headache o physical effort. Examination showed sign of nervous lability and a tendency t

veating; the reflexes were normal and the ood pressure was 100/60 mm. Thus the tacks had changed from acetonemic miting to a migrainous type.

The fifth case concerned a man, aged 3, who had been treated for acetonemic miting at the age of 3. The mother suf- red from typical migraine and also from zema. From the fourth year of life the tacks started with pain around the right e with radiation to the neck, and later so with photophobia. After the age of 5 the attacks subsided. Examination owed nervosity and tendency to sweat- g. The reflexes were normal and the ressure was 120/70 mm. In this case it ems that from the beginning migraine ith relatively protracted subsequent miting rather than acetonemic vomiting ad been dealt with.

Of the total of 24 patients examined suffered from migraine at the time of amination; the material is small but the cidence of migraine is high, as the nor- al incidence is judged at around 6 per nt. Seven out of 22 mothers of the pa- ents had typical migraine, while the gen- al incidence of migraine among Swedish omen between the ages of 30 and 60 mounts to about 15 per cent. The differ- nce is not definitely statistically signifi- nt in view of the small material. Only of 21 fathers suffered from migraine ut it must be stressed that direct inter- gation was only exceptionally afforded.

In the author's material a relationship migraine was much more frequent in oys than in girls, but the material is o small to afford definite conclusions. history of a relative with acetonemic miting was found in only 1 case, but robably similar cases have been overlook- d as the attacks may be interpreted wrong- or forgotten completely. According to ne writer 11 out of 65 children with re- eated attacks of acetonemic vomiting of ore than 24 hours' duration later develop- d migraine, and 44 out of 100 parents f such children suffered from migraine. he differences between these and the uthor's figures are not definitely statisti- lly significant. The fact of an increased cidence of migraine in the families of a atient with acetonemic vomiting obvious- could be interpreted by the fact that oth affections are more frequent in a certain type; namely, that of constitutional nervous instability. Observation of migraine was made in the families of 6 out of 14 patients with acetonemic vomiting, and in 5 of the 6 cases the parents were involved; on roentgenologic examination of the stomach of children with attacks of acetonemic vomiting, hypotonia and marked delay of the gastric evacuation was found, and the author observed the same phenomenon repeatedly during migraine attacks.

Thus a direct relationship between acetonemic vomiting and migraine seems to exist in a small portion of the patients, migraine in the family is observed in a larger group, and a relatively large group shows no relationship to migraine although the latter may in some cases appear later, as the average age on examination was 14, and as definite signs of nervous lability were found in many of them.

Chloromycetin in the Treatment of Pneumonia in Infants and Children. A Preliminary Report on 33 Cases— Recinos, Adrian, Jr., Ross, Sidney, Olshaker, Bennett and Twible, Ellsworth — *New England Journal of Medicine*, 241: 733 (November 10) 1949.

During the winter of 1948-1949, a special pneumonia ward was set up at the Children's Hospital, Washington, D. C., to study the efficacy of chloromycetin in the treatment of pneumonia. During a four month period, 33 patients were treated with chloromycetin.

"A uniform diagnostic work-up was employed in each suspected case of pneumonia. This consisted of an x-ray examination of the chest, complete blood count, nasopharyngeal and blood cultures and agglutinins for streptococcus MG and cold hemagglutinins. After this initial study, repeat chest films, blood counts and nasopharyngeal cultures were taken every two or three days during the course of therapy, and the serologic studies were performed at intervals of 7 to 14 days. Strict clinical and laboratory criteria were employed before a case was included in this study, and any patient who presented equivocal findings on admission was summarily excluded from this series."

"The ages of these children ranged from 4 months to 12 years. Of these, 3 patients were less than 6 months, and 6 ranged from 6 to 12 months, 8 from 1 to 2 years, 5 from 2 to 6 years, and 11 from 6 to 12 years of age.

"The 33 cases in this series, all of which were considered to be bacterial pneumonias, were classified as follows: pneumococcal 18; streptococcal, 1; staphylococcal, 1; and unclassified, 13."

"Twenty of the 33 patients were considered to be markedly ill at the time of admission, and 8 of these required oxygen. Eleven of the remaining 13 were regarded as moderately ill, and the other 2 cases were classified as mild. The temperature at the time of initiation of chloromycetin therapy ranged from 101 to 106° F. In 27 of the 33 cases, it was above 103° F. In 16 patients the white cell count at the time of hospitalization was above 20,000, and in 15 cases it ranged from 10,000 to 20,000. Two other patients showed white cell counts below 10,000. In each patient in this series there was demonstrable x-ray evidence of pneumonia."

"Chloromycetin was administered orally in a dosage ranging from 50 to 220 mg. per Kg. of body weight per 24 hours, or an average of 112 mg. per Kg. per day. The dosage interval was usually every three hours, an occasional patient receiving the drug every four hours. The duration of therapy ranged from two to six days, with an average of four and eight-tenths days per patient. The total dose of chloromycetin ranged from 3.4 to 11.3 Gm., with an average of 5.9 Gm. per patient.

"With reference to the administration of chloromycetin orally, only in the older age group was it possible to administer an intact capsule. In infants and younger children, it was necessary to empty the contents of the capsule and, in view of the extreme bitterness of the drug, to administer it in different vehicles. These included syrup of yerba santa, chocolate milk, chocolate syrup, cherry syrup, applesauce and lemon juice." The writers' experience in this regard indicated that mixing the drug with syrup of yerba santa and following it with chocolate milk was perhaps the best method of administration in small children.

"The therapeutic effect of chloromycetin on the 33 patients with bacterial pneumonia was favorable. The over-all result (based principally on the rapidity of return to normal of clinical, roentgenological and laboratory findings) were considered good in 25 cases, fair in 7 and poor in only 1. In 1 case a relapse occurred a week after the drug had been discontinued, and the patient was retreated with chloromycetin. An uneventful recovery ensued. One patient who had a staphylococcal pneumonia with an associated empyema showed no improvement with chloromycetin after 48 hours. Penicillin and aureomycin were then substituted, but the patient failed to improve until surgical drainage was performed.

"In 20 of the 33 patients the temperature returned to normal within 18 hours of the initiation of chloromycetin therapy. In 7 other patients defervescence was observed 18 to 36 hours after treatment had been started. In 5 of the 6 remaining cases the temperature was normal after 36 to 72 hours. Thus, in 32 of the 33 cases, the temperature was normal within three days of the initiation of therapy. Concomitantly there was striking clinical improvement characterized by prompt relief of the prostration, dyspnea and cough.

"The rapidity of clearing of the nasopharyngeal pathogens following initiation of chloromycetin was observed by the performance of serial nasopharyngeal cultures on each patient. The first culture was obtained at the time of admission, and two to four subsequent cultures were obtained at two day intervals. In 9 of the 18 cases of pneumococcal pneumonia, the organism was not demonstrable after the second day of therapy. In 2 other patients, the organisms had disappeared by the fourth day. In the remaining 7, pneumococci (usually in reduced number) were still demonstrable on nasopharyngeal culture after the fourth day. Of the 4 cases in which *Hemophilus influenzae* was the predominant organism on the initial culture, 3 were negative for this organism two days after chloromycetin therapy had been started. In the case in which a hemolytic streptococcus was the sole organism isolated from the nasopharynx prior to treatment, the organism disappeared two days after therapy had been begun.

"An analysis of the drop in white cell unts revealed that in 21 of the 33 pa-nts the count had returned to normal the third day after the initiation of loromycetin therapy. Of ancillary in-rest was the observation that in several ses the white cell count dropped below 000 three to five days after therapy had en started. However, the leukopenia was t progressive and was not associated with y granulocytopenia. In no case was it cessary to discontinue the drug because the leukopenia. There was no concomi-nt reduction in red cell or platelet count.

"Serial chest x-ray films showed ap-reciable resolution of the inflammatory ocess four to seven days after chloro-ycetin had been started in 24 out of e 33 patients."

cute Laryngotracheobronchitis Treat-ed with Chloromycetin — MON-CRIEFF, A. AND WELLER, S. D. V. — *Lancet*, 2: 748 (October 22) 1949.

"Laryngotracheobronchitis is one of the ost alarming emergencies with which the hildren's physician has to deal. Other cute affections of the respiratory tract sually appear to yield to chemotherapy; t this one, like atypical pneumonia, has pparently been uninfluenced by such eatment. There is some evidence that it caused by a virus.

"Attacking children between 6 months nd 3 years of age, with a sudden onset, ne infection leads rapidly to a critical tate, often necessitating tracheotomy and ronchoscopic suction." Of 6 children, all l enough to require surgical intervention, reated at the authors' hospital since De-ember, 1947, 4 died. On the admission f the seventh case 'chloromycetin' was ied and the result seemed to be dramatic. "Though one of the youngest of the small series and certainly the youngest to survive, this child's state changed rapidly from one of extreme seriousness to one of easy convalescence. All other adjuvant measures were used: the child was nursed in an oxygen tent with 'special' nurses; tracheotomy was performed and suction carried out as required. Chloramphenicol (chloromycetin) was given by mouth in 0.25 Gm. doses three times a day for four days, starting a few hours after the tracheotomy. The thick, tenacious secretion found at tracheotomy in these cases became thin and less profuse than in other cases. Bronchoscopy was only required once, the temperature reached normal in 48 hours, and the tracheotomy tube was removed within five days."

Details of the 7 cases are as follows:

Case	Age	Duration of severely obstructed breathing before tracheotomy	Result
1.	1 year 1 month	24 hours	Died
2.	2 years	3 hours	Lived
3.	10 months	12 hours	Died
4.	9 months	30 hours	Died
5.	2 years 11 months	1 hour	Lived
6.	1 year	36 hours	Died
7.	1 year 3 months	12 hours	Lived

"It will be noted that the children who survived were those in whom tracheotomy was performed early, and chloramphenicol must not be regarded as a substitute for mechanical relief of obstruction at an early stage when required.

"This preliminary note is intended to encourage others to try this new drug for a disease with an unfortunately high fatality rate. It is unlikely always to obviate the necessity for the skilled assistance of surgical colleagues, but it may shorten the whole period of illness and render the infection less virulent."

Symposium Section

Aspirin Poisoning

There is probably no "over the counter" drug which is used more often—and perhaps more indiscriminately—than aspirin even though the antihistaminic cold tablets are now pushing it for first place. It affords prompt relief from so many physical and mental conditions which cause discomfort and impair efficiency that its popularity is understandable. These convenient tablets are commonly gulped down with or without water and the number taken usually depends on how long the individual has been taking them. For this reason it is a "good seller" in any kind of a store, street corner stand, lobby concession and even department drug stores. Ample supplies are kept in medicine cabinets in most homes and in desk drawers in most offices. So it is not difficult to see how easily it becomes habit forming just as does anything else which causes a feeling of well-being and the disappearance of fancied or real distress. Luckily this habit is not as serious an addiction as are other commonly used drugs, but definite and dangerous effects may and do result from the use of aspirin. It is true that it has been used for a long time and so many have escaped its untoward effects. Nevertheless they are real, have a surprisingly wide range and are sometimes frightening.

For generations physicians have relied on the salicylates—and still do—as analgesics in rheumatic conditions but until rather recently no one suggested that they were curative. Naturally there have been many controversial discussions concerning the dosage, means of administration and whether they could be expected to do something other than relieve pain. Their chief handicap has been that they caused gastric irritation and often had to be discontinued until such symptoms subsided. Early in this century the acetylsalicylic acid was introduced and became known by the trade name of aspirin. It was supposed to overcome all of the objections of sodium salicylate and salicylic acid, an it did to some extent. So the popular pra tice to "take an aspirin" was initiated an is still the custom. It soon proved its valu as an analgesic which certainly was fa less harmful than opiates which were use far too frequently and indiscriminately i the early part of the century. Apparentl there was not as much toxicity or loca effects as had been observed previousl with other salicylates because as far a seems to have been recorded, no ill effect were encountered until 1924. In the ligh of evidence in more recent reports, whic are much more frequent, the impression i gained that this may be due to two fac tors. One is that when aspirin first appea ed it was available only in the powdere form and, secondly, because it was no conveniently obtainable by individuals ex cept in a prescription containing vehicle which we now know really minimized th local effects and controlled the dosage. Th tempo of living was not that of the presen time, there were fewer telephones, aspiri tablets were unknown, and the habit, bor of the suggestion to "take an aspirin," wa something to be developed later.

Those who have reviewed the literatur usually started with Balázs'[1] collection o 752 cases of aspirin toxicity and 4 death which resulted from it from 1924 to 192 in Hungary. After that most of the report came from England but in more recen years they have been appearing at varying intervals in America. This suggests tha the toxic effects of aspirin are being recog nized more frequently and are attracting interest. In view of the widespread use of aspirin in tablets, it cannot be said that there is any cause for alarm bu there is reason to believe that cases may be missed because the effects may simulate other toxic conditions. This has

1. Balázs, J.: Über Azetylsalizylsäure (Aspirin)—Vergiftungen, *Med. Klin.*, **26**:1664 (November 7) 1930. Cited by Lipman, B. L., Krasnoff, S. O. and Schless, R. A.: Acute Acetylsalicylic Acid Intoxication, *Am. J. Dis. Child.*, **78**:477 (October) 1949. Also others.

sed one observer to write of its "mim-
of other toxic states."
Basically the clinical pattern followed by
at has been called in the title "aspirin
soning" is about the same as has al-
ys been observed in other salicylates.
pending on the age of the patient, in-
idual idiosyncrasy, sensitivity and dos-
of the drug, the following symptoms
among those elicited: nausea, vomit-
, tinnitus, deafness, headache, sweating
ten profuse), cyanosis of variable de-
e, apathy, lassitude, incoherence, con-
ion, disorientation, restlessness, semi-
porous state and occasionally coma.
y often the presenting symptom is
r hunger" with the distressing deep in-
rations and exaggerated respiratory
rt (hyperpnea). In a very large num-
of the reported cases moderately high
peratures were among the early symp-
ns.
Some form of salicylate poisoning should
suspected if there is a predominance of
of the symptoms in this list but as
ny of them could be present in other
ic states corroborative evidence should
sought. Outstanding in this connection
he hemorrhagic phenomenon which has
n one of the factors which have awak-
d interest in this type of poisoning.
is is a crude but expressive name for it,
it is sometimes called *salicylism*. The
ditions comprising the hemorrhagic
nomenon of salicylism are epistaxis,
natemesis, melena and, indeed, hemor-
ges which may occur anywhere in the
ly. This observation is not new because
1926, Wetzel and Nourse[2] called atten-
n to the fact that mucous membrane
morrhages were common in methylsali-
ate poisoning. It is probable that there
few who in treating young children
e not occasionally found that epistaxis
been a definite indication for the with-
wal of salicylates. So among the many
ent writers there is full agreement with
nigsberger's[3] suggestion that inquiries
out aspirin treatment should be made
all obscure bleeding.
Many articles could be cited by which
hemorrhagic phenomenon caused by
icylates could be forcefully presented.

Wetzel, N. C. and Nourse, J. D.: Wintergreen Poisoning, *Arch. Path. & Lab. Med.*, **1**:182 (February) 1926.
Honigsberger, M.: Aspirin and Gastric Hemorrhage, *Brit. M. J.*, **2**:57 (July 10) 1943.

We think, however, that the most impressive is an explanation of the way salicylates produce hemorrhage brought out by Link and his associates[4,5] in their studies of hemorrhagic sweet clover disease which eventually led to the discovery of dicumarol. They found that dicumarol does not affect the clotting time of blood in vitro but when it is given by mouth or intravenously it does induce hypoprothrombinemia after 24 hours or occasionally longer. This delayed action is why the use of heparin is popular to produce prompt action and dicumarol is used later to maintain the anticoagulant action. Reasons for this delay were sought. Several were thought out. Among these were that dicumarol inhibited prothrombin formation in the liver so that time was needed before the prothrombin level in the blood could fall or it was theorized that dicumarol itself may undergo chemical changes. The second idea was followed through by Huebner and Link and they demonstrated that dicumarol can be qualitatively reduced to salicylic acid. Further study of substances structurally related to dicumarol showed that the only ones having anticoagulant properties are those that presumably yield salicylic acid or an *o*-hydroxybenzoic acid on chemical degradation. Obviously the next step was to test the action of salicylic acid itself. Link and Huebner found that when single doses of salicylic acid are given to rats kept on an artificial diet low in vitamin K, lowering of the prothrombin level in the blood follows; if vitamin K is present hypoprothrombinemia does not develop but if the salicylic acid is given over a long period of time hemorrhages occur. Still salicylic acid, like dicumarol, does not act in vitro.

These observations on the hypoprothrombinemic action of salicylic acid have been reproduced in man by Shapiro and his associates[6] and by Meyer and Howard.[7]

4. Link, K. P. and Huebner, C. F.: Studies on Hemorrhagic Sweet Clover Disease; Hypoprothrombinemia in Rat Induced by Salicylic Acid, *J. Biol. Chem.*, **147**:463 (February) 1943.
5. Huebner, C. F. and Link, K. P.: Studies on Hemorrhagic Sweet Clover Disease, *J. Biol. Chem.*, **138**:529 (April) 1941.
6. Shapiro, S., Redish, M. H. and Campbell, H. A.: Studies in Prothrombin, *Proc. Soc. Exper. Biol. & Med.*, **53**:251 (June) 1943.
7. Meyer, O. O. and Howard, B.: Production of Hypoprothrombinemia and Hypocoagulability of the Blood with Salicylates, *Proc. Soc. Exper. Biol. & Med.*, **53**:234 (June) 1943.

They found that, as in the rat, the simultaneous administration of vitamin K will prevent the fall of prothrombin, although it is known that vitamin K has little influence on dicumarol-produced hemorrhages.

It is especially interesting to this discussion that acetylsalicylic acid was more effective in the production of hemorrhages than salicylic acid. Thus we have rather convincing evidence that salicylic acid, and especially aspirin, is closely related to dicumarol which we use therapeutically as an anticoagulant especially in coronary occlusion. Likewise Link and his associates who developed this anticoagulant simultaneously accounted for the hemorrhagic episodes which have long been recognized as being associated with the administration of salicylates.

In the many case histories recorded in an increasing number of reports these hemorrhagic accidents are vividly presented. Some who may read this could have had them happen in their practice. We have seen them and have been told of many in conversations which we have had with busy practitioners who do not record their experiences for various legitimate reasons. Briefly to illustrate, we have heard of a boy scout who shocked his leaders and fellow scouts by a severe hematemesis and a rather terrorizing passage of red and later tarry stools. Complete diagnostic study revealed nothing to explain this but the history was that this boy had been swallowing aspirin tablets for a long time and had taken many before these symptoms appeared on a camping trip. A similar severe melena occurred in a Sister of Mercy whose habit it was to take at least four aspirin tablets daily. No other reasons for this bleeding could be detected. Then we could discuss many observations which have been made in England where rheumatic states have always been a major problem. In fact the experiences in this country were another factor which aroused general interest in aspirin poisoning.

In 1938 Douthwaite[8] described a case of a middle-aged doctor who had severe melena four or five hours after taking two 5 grain tablets dry before breakfast relieve neuritis. He had had his alimentary tract x-rayed and a gastric analysis a days before. This was, presumably, dur a routine check-up and was entirely co cidental. He had no indigestion and tests had shown no abnormality exc hyperchlorhydria. Twelve days after bleeding, x-rays again showed a norm alimentary tract. This aroused the inter of Douthwaite, who with Lintott und took to investigate a theory which so had concerning the cause of these inc sistently occurring hemorrhages follow aspirin. So they[9] later gastroscoped patients after they had swallowed th crushed aspirin tablets in an ounce water, and compared the appearances w those in 5 patients who had swallow barium sulfate. In 13 patients, the aspi produced a localized inflammatory re tion, ranging from slight to intense hyp emia and even submucous hemorrha No reactions were seen in the patie receiving barium sulfate. Five patie were given 15 grains of calcium acetyls icylate. In 3, the drug dissolved so w that no particles were seen and there we no mucosal reactions. In the other 2, so particles were seen, and 1 of these patie showed slight localized hyperemia.

Following this Hurst and Lintott[10] pu lished a striking example of the irritati effect of aspirin in a sensitive subject. man, age 57, had two severe attacks melena and one of hematemesis as well other evidence suggestive of internal blee ing, over a period of 13 years. Thr months after the last attack, no eviden of ulcer, blood dyscrasia, or other cau of bleeding could be found. The man, ho ever, had been taking at least six aspir tablets a day uncrushed and without wat for many years, to relieve his migrain Gastroscopy was performed immediate after he swallowed two aspirin tablet broken but not crushed. Within a fe minutes the mucosa around the fragmen became intensely hyperemic, and e travasated blood was seen staining t

8. Douthwaite, A. H.: Some Recent Advances in Medical Diagnosis and Treatment, *Brit. M. J.*, **1**:1143 (May 28) 1938.

9. Douthwaite, A. H. and Lintott, G. A. M.: Gastroscopic Observations of Effect of Aspirin a Certain Other Substances on Stomach, *Lancet*, 1222 (November 26) 1938.

10. Hurst, A. and Lintott, G. A. M.: Aspirin as Cause of Haematemesis: Clinical and Gastroscop Study, *Guy's Hosp. Rep.*, **89**:173 (April) 193

gments red. There was no further bleed- when aspirin and salicylates were for- den. In a later report Hurst[11] strongly ed that the label of every bottle of irin tablets should carry instructions t they must be taken powdered and r food and that the maximum dose uld be 10 grains.

As has been previously suggested the glish reports in the early part of this ade may have alerted many on this e of the Atlantic to the possibility of irin effects. In any event there have n more articles in American journals e then. However, there is one factor ch is mentioned specifically in several these articles which has been largely reason for more reports in this country. 1943 Coburn[12] suggested that if sodium cylate was given early and administered ravenously in doses large enough to duce a blood concentration of 35 mg. 100 ml., salicylates have a curative ion and they will prevent the develop- nt of cardiac involvement. Because the cylates had been used for so long and so wide a range of doses and because cylism had long been accepted, this m was received with no small amount skepticism especially among older ups. In any event Coburn's suggestion been followed by many, but his hopes definite curative effects have not been lized, and as far as we can find Peters,[13] been the only one to support the idea.

In America, Fashena and Walker,[14] vens and Kaplan,[15] Krasnoff and Bern- n,[16] Dubow and Solomon[17] and others are among those who have reported on salicylate intolerance and toxicity which resulted from large therapeutic doses. It was from these sources that still another phase of salicylate intoxication has been obtained. This is the definite bicarbonate acidosis and ketosis which has often been the cause of the deaths. The best description of this phase is given in an article by Alexis Hartmann[18] whose qualifications to discuss it need no emphasis.

He was impressed in his studies of 7 infants and one 4 year old child with the primary hyperventilation caused by central stimulation. This leads to a CO_2 deficit type of alkalosis with alkaline urine and moderate compensatory reduction in blood bicarbonate. Then ketosis develops to the extent that in 1 of his cases a hypoglycemia developed. This produces a real bicarbonate deficit acidosis, with a shift to acid urine. He found that this ketosis cannot be immediately abolished by the usual administration of glucose or glucose and insulin and may last four or five days. He suggests "neutralization" with repeated injections of Na-lactate or sodium bicarbonate. He prefers the Na-lactate because of its glycogenic properties, its greater safety, and its ease of administration. He contends that even after ketosis is abolished, salicylates may still be found in the body fluids and the distressing "air hunger" (hyperpnea) may still remain with the rather disturbing exaggeration in the respiratory efforts. So to many this means central damage, especially when it fails to respond to the measures outlined by Hartmann. For corroboration we have but to refer to the report of Ryder, Shaver and Ferris,[19] whose complete study of a case of salicylism was of special interest because the drug had been given to a 16 year old Negro girl in the usual doses, as determined by symptomatic effect. Their outline of the clinical and laboratory observations answered all questions which could possibly arise in the minds of anyone. The course of the intoxication was clearly shown by studies of the acid-base balance, to be a respiratory alkalosis. The

11. Hurst, A.: Aspirin and Gastric Haemorrhage, *Brit. M. J.*, **1**:768 (June 19) 1943.
12. Coburn, A. F.: Salicylate Therapy in Rheumatic Fever; Rational Technique, *Bull. Johns Hopkins Hosp.*, **73**:435 (December) 1943.
13. Peters, J. T.: The Necessity and Possibility of Giving Detoxified Large Oral Doses of Salicylates in the Treatment of Rheumatic Fever in Order to Prevent or Cure the Inflammatory Stage of Carditis, *Acta med. Scandinav.*, **128**:51 (June 2) 1947. Abstracted *Internat. M. Digest*, **52**:356 (June) 1948. Also see Editorial, Salicylates in Rheumatic Fever, *Internat. M. Digest*, **52**:373 (June) 1948.
14. Fashena, Gladys J. and Walker, J. N.: Salicylate Intoxication. Studies on the Effects of Sodium Salicylate on Prothrombin Time and Alkali Reserve, *Am. J. Dis. Child.*, **68**:369 (December) 1944.
15. Stevens, D. L. and Kaplan, D. B.: Salicylate Intoxication in Children, *Am. J. Dis. Child.*, **70**:331 (November-December) 1945.
16. Krasnoff, S. O. and Bernstein, M.: Acetylsalicylic Acid Poisoning, *J. A. M. A.*, **135**:712 (November 15) 1947.
17. Dubow, E. and Solomon, N. H.: Salicylate Tolerance and Toxicity in Children, *Pediatrics*, **1**:495 (April) 1948.
18. Hartmann, A. F.: Acute Salicylate Poisoning, *J. Pediat.*, **26**:214 (March) 1945.
19. Ryder, H. W., Shaver, M. and Ferris, E. B., Jr.: Salicylism Accompanied by Respiratory Alkalosis and Toxic Encephalopathy. Report of a Fatal Case, *New England J. Med.*, **232**:617 (May 24) 1945.

case came to autopsy and the anatomic diagnosis in addition to the expected extensive rheumatic heart disease showed evidence of nonspecific toxic encephalopathy.

Aside from the measures suggested by Hartmann there is little to be offered in the treatment of aspirin or other salicylate poisoning. If a large number of tablets have been taken for suicidal intent lavage is, of course, indicated if there is any reason to believe the tablets can be retrieved from the stomach. Paradoxic as it may seem Hartmann contends that suicidal attempts have been failures despite ingestion of large quantities of salicylate drugs. The experience seems to be quite general that no close relationship between dosage and symptoms exists, but experimental observations indicate that with blood concentrations which are likely to be obtained during "intensive" therapy, toxicity may result without the requirement of any unusual individual susceptibility.

Summarily, it may be concluded that aspirin and sodium salicylate are still useful analgesic drugs when they are not abused. They are useful for the relief of pain in many conditions and are definitely safer than opium and other drugs about which less is known because of their rapid passage through the pharmacologic laboratory. There is no proof that any salicylate possesses curative value for any disease state.

Nevertheless ample evidence has been brought forth to show that any salicylate occasionally is capable of producing toxic effects which may cause death. Hartmann[18] contends that 50 per cent of the infants or young children admitted to hospitals for the treatment of salicylism may be expected to die.

It is probably misleading to use the title "aspirin poisoning" too often because the symptoms caused by any other salicylates are similar if not identical. It is true that many of the papers have this title because the case or cases reported were directly due to aspirin, but since the "intensive" treatment of rheumatic fever has been advocated many papers have appeared in which sodium salicylate caused the toxicity. From these our knowledge of salicylism in general has been greatly enhanced. Even though these studies w the result of effects observed after la doses, they confirmed previous experie obtained in aspirin toxicity, that the dos is not always a precipitating factor. I instance Hartmann[18] calls attention to fact that suicidal attempts have often b failures despite ingestion of large quan ties of the salicylate drugs. Specific stances of complete recovery after the sw lowing of 150 five grain tablets[20] and 25 five grain tablets confirm his contention.

Some of the precautionary measu which have been evolved from these o servations are as follows:

More information should be disse nated concerning the danger which is p sible from the routine and indiscrimina use of aspirin.

More emphasis should be placed on t importance of not swallowing the dry ta lets without the aid of a glass of water.

The suggestion to powder the tabl with the blade of a knife and then to su pend this powder in a glass of water shou be offered.

The dissolution of the tablet in a gla of water is possible with some aspi tablets. This is accomplished by droppi the tablet in a glass of water. It may th be sipped and agitated between sips b cause the aspirin is still in suspension a is not dissolved as it is commonly believ to be.

It should be remembered that aspir given internally and/or applied locally the tonsillar fossa after tonsillectomy h been known to cause hemorrhage.[22]

The extensive use of aspirin or salicy ates in all cases of bleeding which cann be definitely attributed to other caus should always be ruled out.[3] Especially this indicated in melena, hematemesis a epistaxis.

Meyer and Howard[7] suggest that vita min K be administered in cases in whic salicylate treatment is to be given over long period, despite the fact that vitami K has little influence on dicumarol-pr duced hemorrhages.

20 Charters, A. D.: A Case of Aspirin Poisonin *Brit. M. J.*, **1**:10 (January 1) 1944.
21. Hopkins, P.: Aspirin Poisoning. Report of Case, *Lancet*, **1**:145 (February 3) 1945.
22. Singer, R.: Acetylsalicylic Acid, Probable Cau for Secondary Post-Tonsillectomy Hemorrhag Preliminary Report, *Arch. Otolaryng.*, **42**:1 (July) 1945.

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Moth Ball Anemia

When it was reported from two cities in country a few years ago that a rather e number of underprivileged humans ng as squatters on the city dumps had uired lead poisoning as a result of ning wooden battery cases as fuel, it thought for a long time that this was ally unique way of getting into physi- trouble. The diagnosis of lead poison- was unequivocal as the x-ray evidence he deposition of lead in the bones was te clear. The source of the lead was a tery and it was only after consider- e medical sleuthing around the squalid cks built from dump-salvaged materials t the battery case fuel was discovered. s fuel burned fiercely and gave off h heat. It also gave off lead which volatilized from the impregnated wood a result of the combustion. This was aled from the air of the poorly ventilat- hovels by the inmates and they ac- red lead poisoning in a way which had been recognized but never so fantas- lly illustrated. Shortly after the same g occurred in another city but as far we know it has never happened again. s is doubtless due to the fact that tery cases are no longer made of wood.

However, new ways of getting into physi- trouble crop up with startling regular- to replace those which are eliminated which are avoided for a few years until warnings are forgotten or are unknown new generations. It is always desirable call attention to avoidable dangers so we are repeating some details of 4 accidents which happened in Detroit recently. They were reported from the Anemia Clinic of Michigan Children's Hospital and the Department of Pediatrics of Wayne University College of Medicine.

These accidents, as they may be called, were acute emergencies in 4 Negro children who developed acute symptoms suggesting the ingestion of some poison. The report of the most thorough study of these cases is conveniently available and reveals a cause of anemia which apparently is not generally known and not even suspected. It was made by Dr. Zuelzer and Dr. Apt[1] of the Wayne University Medical School and again there are indications that some medical sleuthing was necessary to discover the cause of the anemia which their comprehensive study showed would have been indistinguishable from the so-called Lederer's anemia if it had not been found to be due to moth balls.

Four children ranging in age from 2 to 2½ years were admitted with similar symptoms which consisted of nausea, vomiting, elevated temperature, diarrhea and hemoglobinuria as evidenced by the passage of urine described as being the color of port wine. Complete histories are presented in the original study of these cases and it was only after close questioning in two of the cases that a father in one and a neighbor in the other revealed that they had discovered the children sucking on moth balls.

Zuelzer and Apt then studied the anemia which followed in all of these cases and compared it with the results of ingested moth balls in three dogs. What they record is most interesting reading which is strongly recommended.

Naphthalene, of course, is of what the little balls are made. They are glistening white little objects which are fascinating to any 2 year old and are easier to put into the mouth than a dirty slipper. They have been around all homes for years and it seems incredible that a diligent search by these two experienced workers revealed no report of this happening before in America. They did find that most of the

1. Zuelzer, W. W. and Apt, L.: Acute Hemolytic Anemia Due to Naphthalene Poisoning, *J. A. M. A.*, **141**:185 (September 17) 1949.

standard textbooks on pediatrics stated that naphthalene is not soluble, passes through the digestive tract without absorption and is therefore harmless. But they found that textbooks on toxicology refer to cases described in the foreign literature in which gastrointestinal and neurologic symptoms and anemia followed the ingestion of naphthalene.

The cases followed a course similar to those in the 4 children. The source of the naphthalene in these cases, most of which were reported from Africa, India, Brazil and continental Europe,* was occasionally from moth balls but the poisoning also resulted from the administration of naphthalene in the treatment of roundworms (oxyuriasis).

Zuelzer and Apt have taken advantage of their opportunity to clarify naphthalene poisoning. Their clinical study helped to do this but they went further by instituting animal experiments. By these they found that there is little doubt that naphthalene is a toxic substance capable of being absorbed and of producing an anemia of the hemolytic type. The sequence of events, such as the appearance of Heinz bodies in the erythrocytes preceding a sharp fall in hemoglobin, hematocrit and red blood count; fragmentation of erythrocytes; leukocytosis and reticulocytosis, and subsequent restoration of the blood values to normal levels, they consider as fulfiling the characteristic effect of a hemolytic poison comparable to the well known action of phenylhydrazine.

Each of the 4 patients had a definite history of naphthalene ingestion, in 1 case absorption was demonstrated by isolating naphthalene derivatives in the urine, each child had previously been in perfect health, none of them had been exposed to other chemicals with hemolytic action and all of them made complete recoveries.

As has been implied the general picture in the blood of these children is strikingly like the so-called Lederer's anemia into which category all acute hemolytic anemi are often placed. So these investigato say that had the information concerni naphthalene not been obtained, each ca undoubtedly would have been label Lederer's anemia. So their suggestion th it is likely that some cases reported in t literature under that title were in reali naphthalene poisoning seems plausible.

The diagnosis of naphthalene poisonin of course, depends primarily on an acc rate history. It also may be expected occur in the age group around 2 yea when the tendency to ingest househo poisons is greatest. The symptoms pr viously outlined should be regarded wi suspicion and the absence of splenomega and icterus in the cases in Detroit w considered significant. The laboratory r sults are those of severe hemolytic anem and hemoglobinuria. Free hemoglobin demonstrable in the plasma in the acu stage. Fragmentation of red blood ce and the presence of Heinz bodies are cha acteristic features of toxic hemolysis. addition to hemoglobin, albumin, occasio al leukocytes and granular casts, an odor naphthalene should be looked for in su pected cases.

The treatment of the condition does n include splenectomy as has been performe under similar circumstances. The treatmer of choice consists of transfusions whic were used in the 4 cases. All of them r sponded favorably to this and were o of the hospital after an average of tw weeks.

In any event the condition in this cou try may be expected to occur chiefly i children in the early age groups and unle the moth balls are put out of reach wit the lye, rat and roach poison, matche razor blades, open safety pins, etc., th may happen again. It is still strange tha these are the first cases reported and tha they should have occurred in a group i Detroit. The only plausible explanation that they must have been missed. But no that Zuelzer and Apt have given us suc a comprehensive paper on the subject the never should be missed again—at least i the present generation.

* Since this has been written a case which had not been previously recorded is reported from England. It is discussed in "Letters to the Editor" of the *Lancet*, **2**:964 (November 19) 1949 by Dr. George Newns.